Access DB# 77850

521

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: SUDHAKER PATEL Examiner # : 77018 Date: 10/11/02
Art Unit: 1624 Phone Number 30 84709 Serial Number: 10016280
Mail Box and Bldg/Room Location: CM1 4E17 Results Format Preferred (circle): PAPER DISK E-MAIL
4E12

If more than one search is submitted, please prioritize searches in order of need. mej

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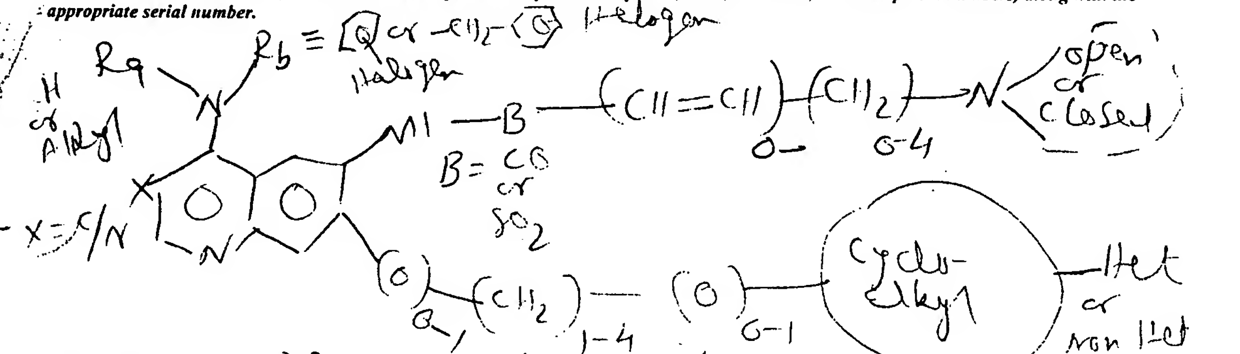
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: BICYCLIC HETEROCYCLES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS, THEIR USE & PROCESSES FOR PREPARING THEM

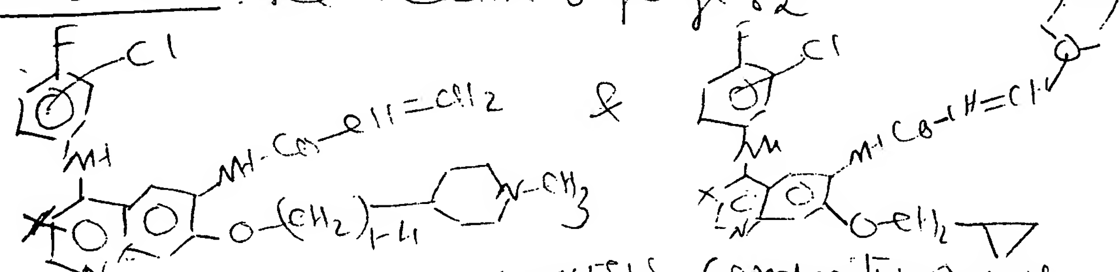
Inventors (please provide full names): FRANK HIMMELSBACH et al

Earliest Priority Filing Date: 6/21/1999

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*



TYPICAL CPDS: see claim 6 page 82



Need info @ cpds, THEIR SYNTHESIS, Composition & use as inhibitors of TYROSINE KINASE
Need: all bib but cpds listed in CAPLUS. Copy of claims enclosed THX

** 1624

STAFF USE ONLY		Type of Search		Vendors and cost where applicable	
Searcher:		NA Sequence (#)		STN	
Searcher Phone #:	308-4499	AA Sequence (#)		Dialog	
Searcher Location:		Structure (#)		Questel/Orbit	
Date Searcher Picked Up:		Bibliographic		Dr.Link	
Date Completed:	10/17/02	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:		Fulltext		Sequence Systems	
Clerical Prep Time:		Patent Family		WWW/Internet	
Online Time:		Other		Other (specify)	

PTO-1590 (8-01)

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 16:05:03 ON 17 OCT 2002
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FILE COVERS 1907 - 17 Oct 2002  VOL 137 ISS 16
FILE LAST UPDATED: 16 Oct 2002  (20021016/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

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L8              STR
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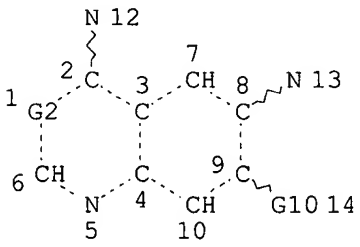


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DEFAULT ECLEVEL IS LIMITED

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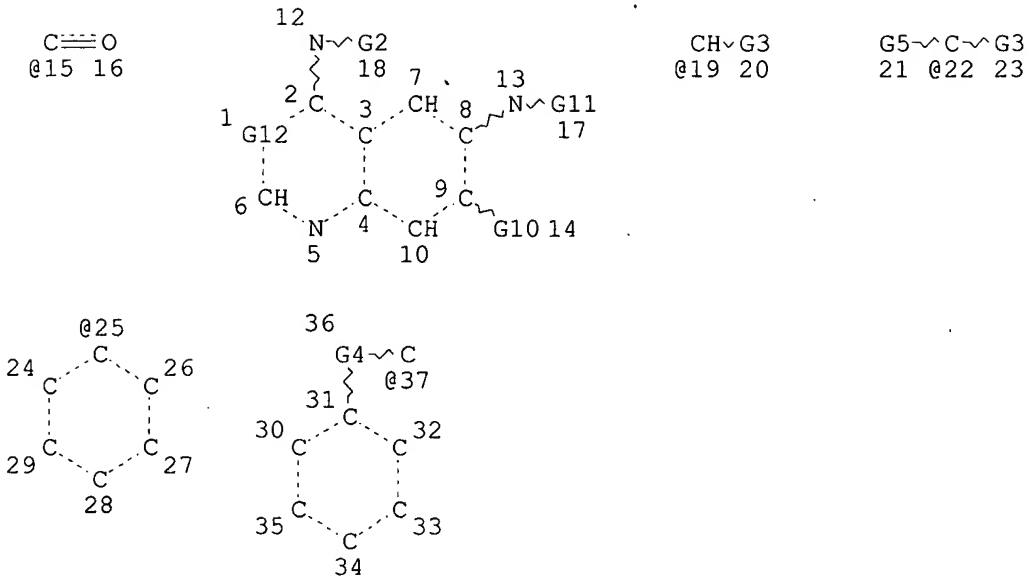

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STEREO ATTRIBUTES: NONE
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L15 9 SEA FILE=HCAPLUS ABB=ON PLU=ON L14

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=> d ibib abs hitstr tot l15

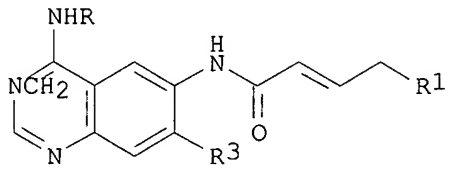
L15 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:487536 HCAPLUS
DOCUMENT NUMBER: 137:63250
TITLE: Quinazoline derivatives as inhibitors of human EFG tyrosine kinase
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Blech, Stefan; Jung, Birgit; Baum, Elke; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050043	A1	20020627	WO 2001-EP14569	20011212
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10063435	A1	20020704	DE 2000-10063435	20001220

PRIORITY APPLN. INFO.: DE 2000-10063435 A 20001220

OTHER SOURCE(S): MARPAT 137:63250

GI



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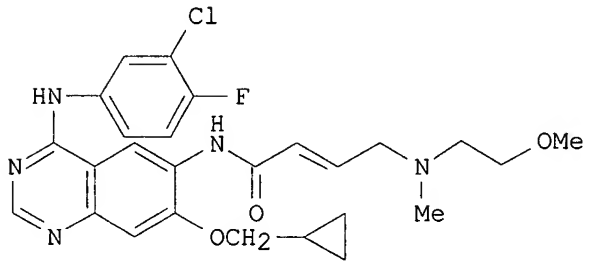


II

AB Quinazoline derivs. I [R = PhCH2, PhCHMe, 3,4-Cl(F)C6H3; R1 = NMeR2, NEt2, NEtCH2CH2OMe, N(CH2CH2OMe)2, morpholino; R2 = Me, Et, CHMe2, cyclopropyl, CH2CH2OMe, 3-tetrahydrofuryl, 2-tetrahydrofurylmethyl, 3-tetrahydrofurylmethyl, 4-tetrahydropyranyl, 4-tetrahydropyranylmethyl; R3 = cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, 3-tetrahydrofuranyloxy, 2-tetrahydrofuranylmethoxy, 3-tetrahydrofuranylmethoxy, 4-tetrahydropyranyloxy, 4-tetrahydropyranylmethoxy] were prepd. for use as inhibitors of signal transduction caused by human EFG receptor tyrosine kinase. They are useful in the treatment of tumoral diseases, diseases of the lung and the respiratory tract, the gastrointestinal tract, and the gallbladder and bile ducts. Thus, the quinazoline II was prepd. by converting bromocrotonic acid to its chloride, and reaction with 4-[(3-chloro-4-fluorophenyl)amino]-6-amino-7-cyclopropylmethoxyquinazoline, followed by MeNHCH2CH2OMe. II had an IC50 against human EFG receptor kinase of 0.7 nM.

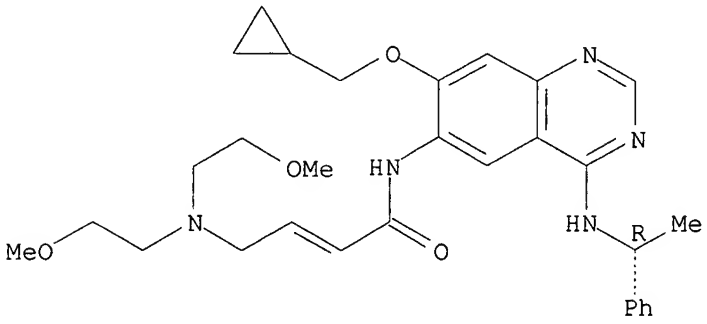
IT **439081-11-5P 439081-13-7P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of quinazoline derivs. as inhibitors of human EFG tyrosine kinase)

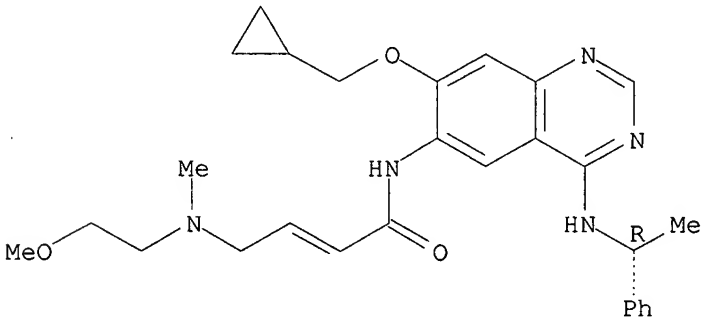
RN 439081-11-5 HCAPLUS
CN 2-Butenamide, 4-[bis(2-methoxyethyl)amino]-N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



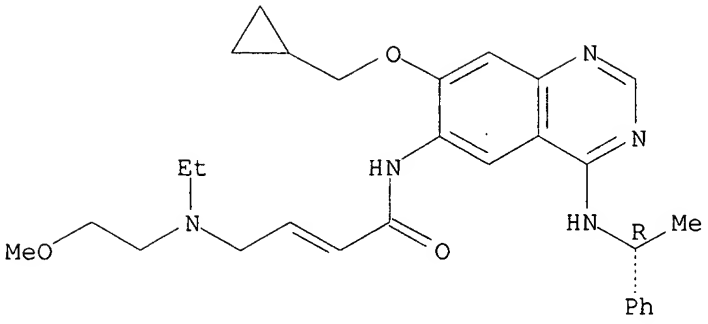
RN 439081-13-7 HCAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[(2-methoxyethyl)methylamino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



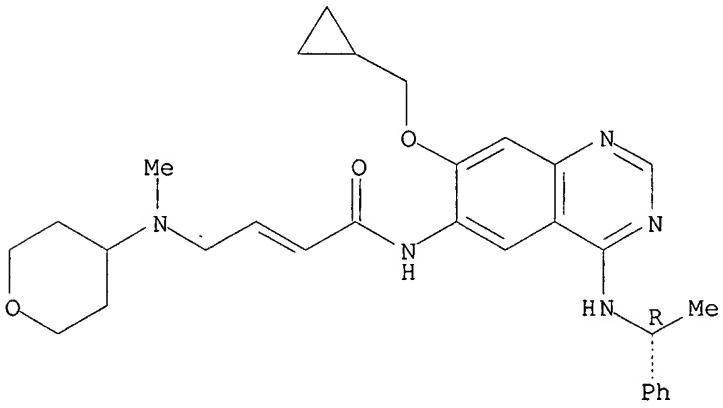
IT **439081-12-6P 439081-14-8P 439081-15-9P**
439081-23-9P 439081-29-5P 439081-33-1P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazoline derivs. as inhibitors of human EFG tyrosine kinase)
RN 439081-12-6 HCAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[ethyl(2-methoxyethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



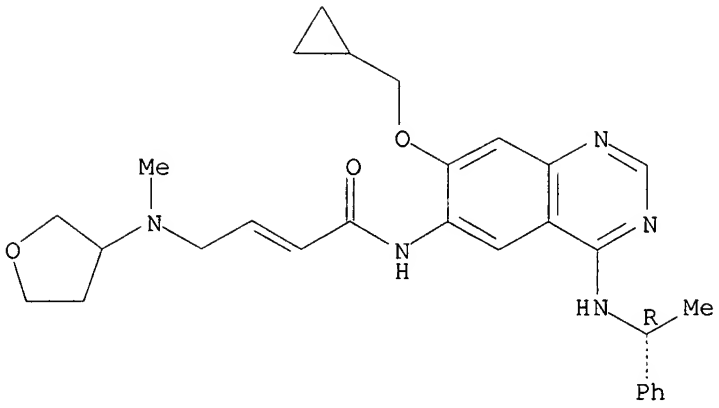
RN 439081-14-8 HCAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[methyl(tetrahydro-2H-pyran-4-yl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



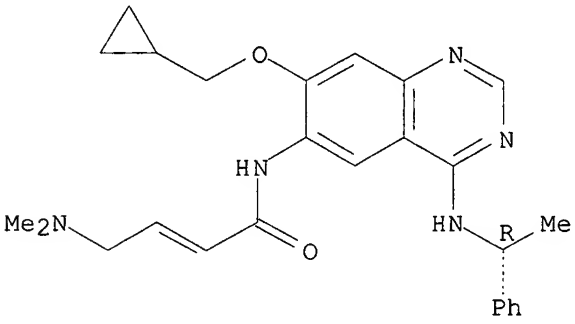
RN 439081-15-9 HCAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[methyl(tetrahydro-3-furanyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



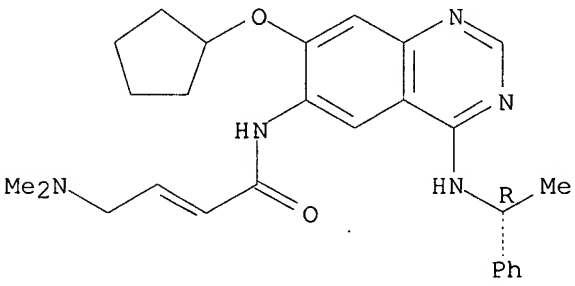
RN 439081-23-9 HCAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



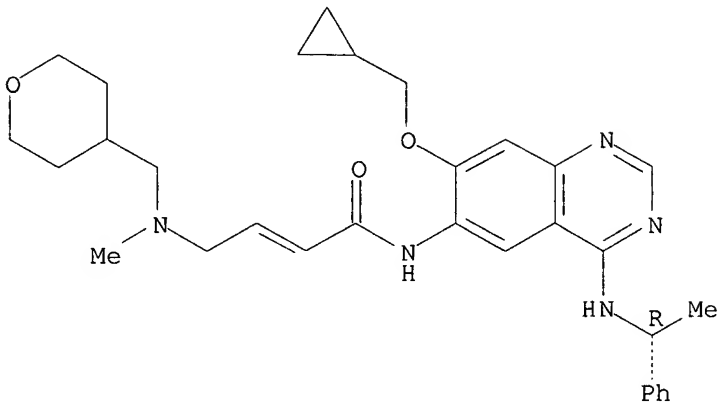
RN 439081-29-5 HCAPLUS
CN 2-Butenamide, N-[7-(cyclopentyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 439081-33-1 HCAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[methyl[(tetrahydro-2H-pyran-4-yl)methyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:314395 HCAPLUS
DOCUMENT NUMBER: 136:335540
TITLE: Use of PDE V inhibitors for improved fecundity in mammals
INVENTOR(S): Westbrook, Simon Lempriere; Zanzinger, Johannes Friedrich
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

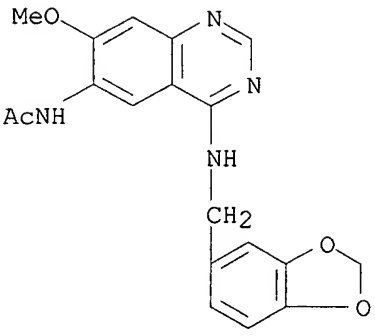
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1199070	A2	20020424	EP 2001-308684	20011011
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2002220346	A2	20020809	JP 2001-322195	20011019

PRIORITY APPLN. INFO.: GB 2000-25782 A 20001020

AB The invention relates to the use of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type five (cGMP PDE V) inhibitor for increasing fecundity in a mammal by one or more of (a) promoting the growth of an oocyte, zygote, blastocyst, embryo and/or fetus, (b) increasing the rate or probability of survival of an embryo and/or fetus and (c) increasing the birth wt. of a progeny, or for increasing milk productivity. I.v. and tablet formulations are exemplified. Formulations and packs contg. the PDE V inhibitors for pharmaceutical or veterinary use are claimed.

IT **150450-69-4**
RL: AGR (Agricultural use); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of PDE V inhibitors for improved fecundity in mammals)

RN 150450-69-4 HCAPLUS
CN Acetamide, N-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-7-methoxy-6-quinazolinyl]- (9CI) (CA INDEX NAME)



L15 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:171891 HCAPLUS
DOCUMENT NUMBER: 136:216761
TITLE: Preparation of 4-amino-6-vinylcarbonylaminoquinazoline s as epidermal growth factor receptor signal transduction inhibitors
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018375	A1	20020307	WO 2001-EP9534	20010818
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AU 2002010444	A5	20020313	AU 2002-10444	20010818
US 6403580	B1	20020611	US 2001-935498	20010823

PRIORITY APPLN. INFO.: DE 2000-10042064 A 20000826
US 2000-230541P P 20000905
WO 2001-EP9534 W 20010818
OTHER SOURCE(S): MARPAT 136:216761
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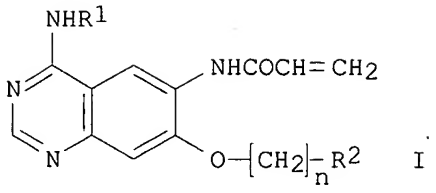


I

AB Title compds. [I; R1 = PhCH2, 1-phenylethyl, (substituted) Ph; R2 = N-(2-oxotetrahydrofuran-4-yl)methylamino, N(CH2CO2R3)2, (substituted) R4OCOCH2NCH2CH2OH, 2-oxomorpholin-4-yl; R3 = H, Me, Et; R4 = H, alkyl; n = 2-4],were prepd. Thus, a mixt. of CH2:CHCO2H and Et3N was stirred for 1 h at -50.degree. with CH2:CHCO2Cl in THF followed by addn. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-oxomorpholin-4-yl)propyloxy]quinazoline (prepn. given) in THF at -55.degree. and slowly heating up at 0.degree. up to completely conversion to give 60% 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-oxomorpholin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. One of the exemplified examples, 4-[(R)-(1-phenylethyl)amino]-7-[2-(2,2-dimethyl-6-oxomorpholin-4-yl)ethoxy]-6-[(vinylcarbonyl)amino]quinazoline, inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.4 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402724-03-2P 402724-07-6P**

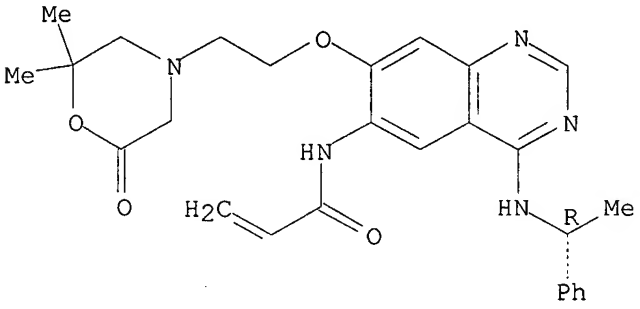
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402724-03-2 HCAPLUS

CN 2-Propenamide, N-[7-[2-(2,2-dimethyl-6-oxo-4-morpholinyl)ethoxy]-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

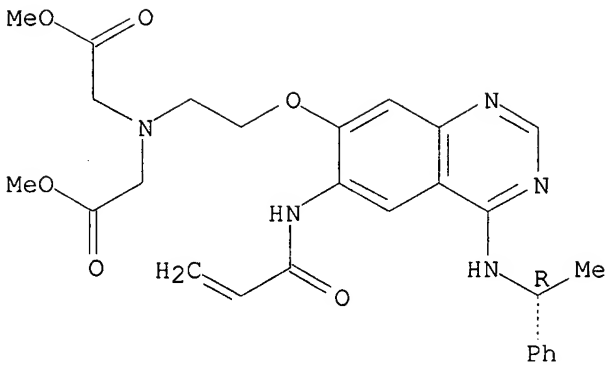
Absolute stereochemistry.



RN 402724-07-6 HCAPLUS

CN Glycine, N-(2-methoxy-2-oxoethyl)-N-[2-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:171889 HCAPLUS
DOCUMENT NUMBER: 136:232315
TITLE: Preparation of 4-amino-6-vinylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018373	A1	20020307	WO 2001-EP9537	20010818
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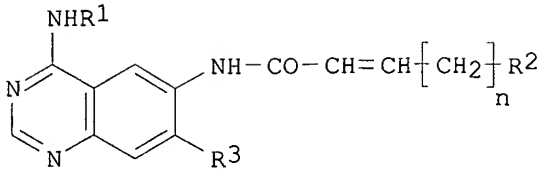
DE 10042060	A1	20020307	DE 2000-10042060	20000826
US 2002077330	A1	20020620	US 2001-929931	20010815
AU 2001084021	A5	20020313	AU 2001-84021	20010818

PRIORITY APPLN. INFO.:
DE 2000-10042060 A 20000826
US 2000-230389P P 20000906
WO 2001-EP9537 W 20010818

OTHER SOURCE(S): MARPAT 136:232315
GI



I

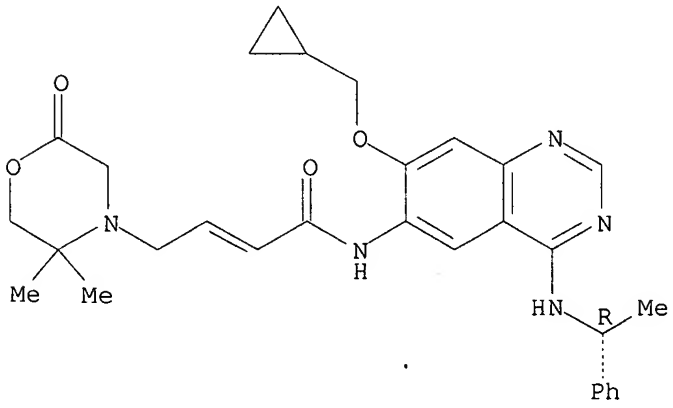
AB Title compds. [I; R1 = PhCH2, 1-phenylethyl, (substituted) Ph; R2 = N-[(1,3-dioxolan-2-yl)methyl]methylamino, (substituted) R4OCOCH2NCH2CH2OH, 2-oxomorpholin-4-yl; R4 = H, alkyl; R3 = H, (alkoxy)alkoxy, cycloalkylalkoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy; n = 1-3], were prepd. Thus, a mixt. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopropylmethoxyquinazoline (prepn. given) and disopropylethylamine in THF was dropwise treated under ice-cooling with BrCH2CH:CHCO2Cl (prepn. given) in CH2Cl2 followed by stirring for 1 h under ice-cooling and for 2 h at room temp. and addn. of (S)-(2-hydroxypropylamino)acetic acid tert-Bu ester in CH2Cl2 to give after stirring over night at room temp. and stirring for 5 h at 60.degree. 64% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[N-(tert-butyloxycarbonylmethyl)-N-((S)-2-hydroxyprop-1-yl)amino]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. Several I inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.02-15 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402855-30-5P 402855-36-1P 402855-45-2P**
402855-50-9P 402855-61-2P 402855-69-0P
402855-72-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402855-30-5 HCAPLUS

CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

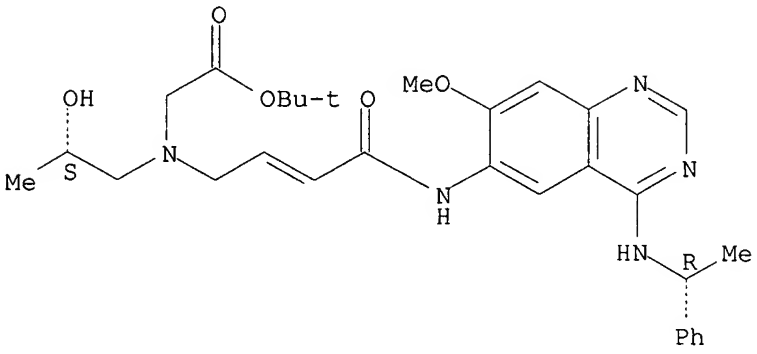


RN 402855-36-1 HCAPLUS

CN Glycine, N-[(2S)-2-hydroxypropyl]-N-[4-[[7-methoxy-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-,

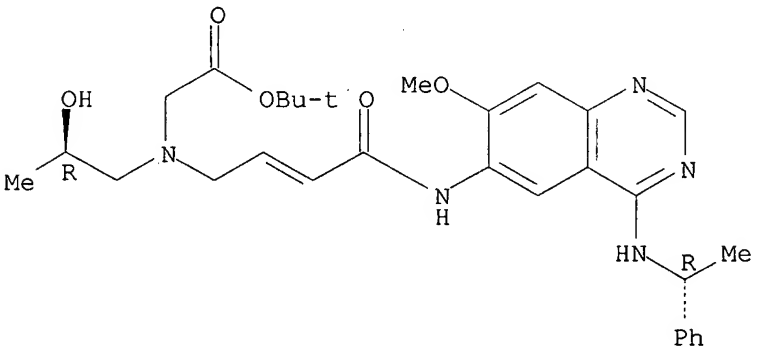
1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



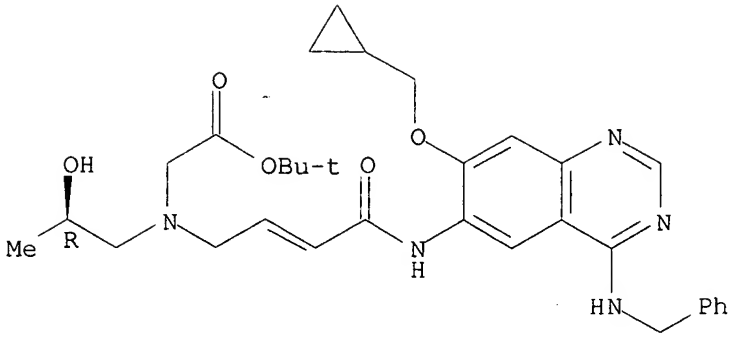
RN 402855-45-2 HCAPLUS
CN Glycine, N-[(2R)-2-hydroxypropyl]-N-[4-[[7-methoxy-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



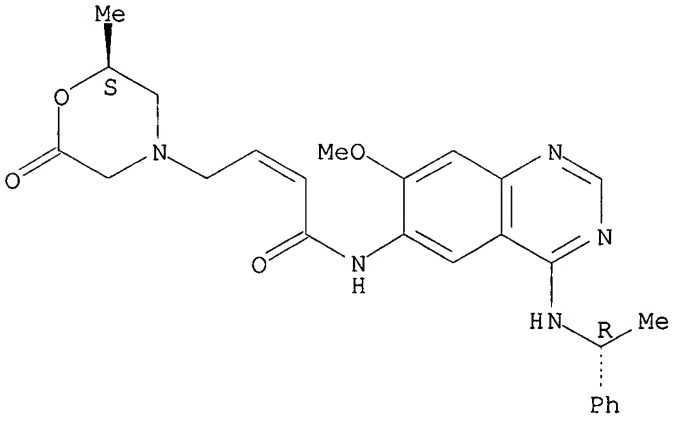
RN 402855-50-9 HCAPLUS
CN Glycine, N-[4-[[7-(cyclopropylmethoxy)-4-[(phenylmethyl)amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



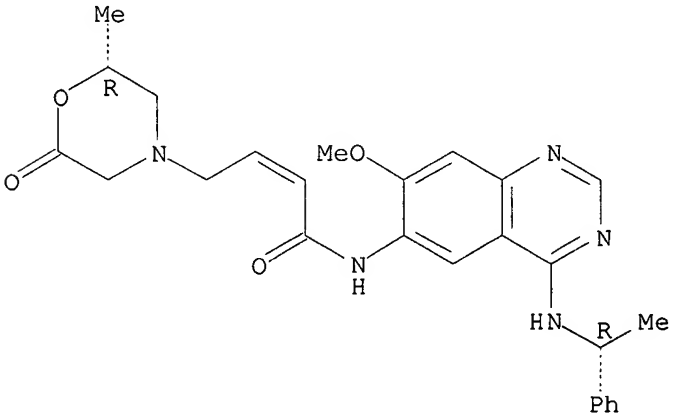
RN 402855-61-2 HCAPLUS
CN 2-Butenamide, N-[7-methoxy-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[(2S)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



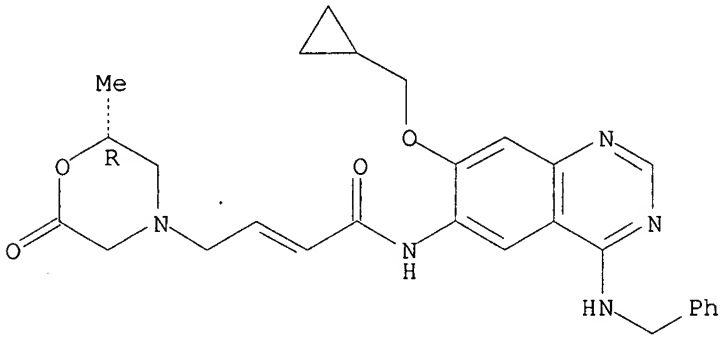
RN 402855-69-0 HCAPLUS
CN 2-Butenamide, N-[7-methoxy-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 402855-72-5 HCAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[(phenylmethyl)amino]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

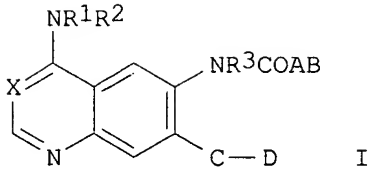


REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:171886 HCAPLUS
DOCUMENT NUMBER: 136:216758
TITLE: Preparation of 4-amino-6-heterocyclylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018370	A1	20020307	WO 2001-EP9535	20010818
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10042061	A1	20020307	DE 2000-10042061	20000826
AU 2001089814	A5	20020313	AU 2001-89814	20010818
US 2002082270	A1	20020627	US 2001-934753	20010822

PRIORITY APPLN. INFO.: DE 2000-10042061 A 20000826
US 2000-230119P P 20000905
WO 2001-EP9535 W 20010818
OTHER SOURCE(S): MARPAT 136:216758
GI



I

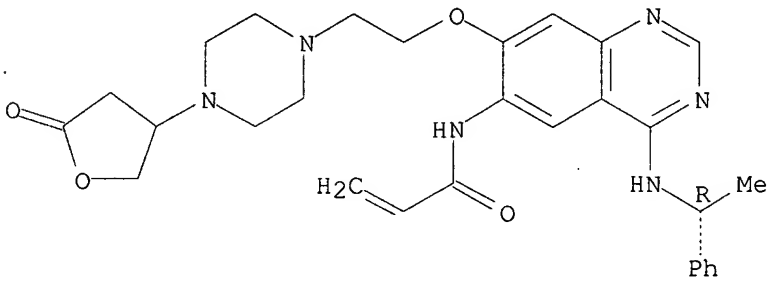
AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH2, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = H, (substituted) alkyl, alkylcarbonyl, CO2H, alkoxycarbonyl, aminocarbonyl, (di)alkylaminocarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, morpholinocarbonyl, alkylpiperazinylcarbonyl; C = (oxy)alkenyl, O; D = (substituted) pyrrolidinyl, piperidinyl, hexahydroazepinyl, piperazinyl, etc.], were prepd. Thus, a mixt. of CH2:CHCO2H and Et3N was stirred for 45 min at -50.degree. with CH2:CHCO2Cl in THF followed by dropwise addn. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl]propyloxy)quinazoline (prepn. given) in THF for 20 min and stirring at 0.degree. up to completely conversion to give 31% 4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl]propyloxy)-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 12 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402496-86-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402496-86-0 HCAPLUS

CN 2-Propenamide, N-[4-[[(1R)-1-phenylethyl]amino]-7-[2-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:911231 HCAPLUS
DOCUMENT NUMBER: 134:71599
TITLE: Preparation of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors.
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Metz, Thomas;

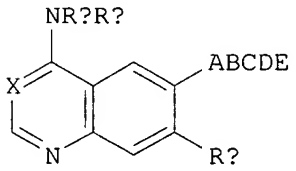
Solca, Flavio; Jung, Birgit; Baum, Anke
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078735	A1	20001228	WO 2000-EP5547	20000616
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19928281	A1	20001228	DE 1999-19928281	19990621
DE 10023085	A1	20011115	DE 2000-10023085	20000511
BR 2000011834	A	20020312	BR 2000-11834	20000616
EP 1194418	A1	20020410	EP 2000-936888	20000616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001006185	A	20011218	NO 2001-6185	20011218

PRIORITY APPLN. INFO.:
DE 1999-19928281 A 19990621
US 1999-146644P P 19990730
DE 2000-10023085 A 20000511
WO 2000-EP5547 W 20000616

OTHER SOURCE(S): MARPAT 134:71599
GI



I

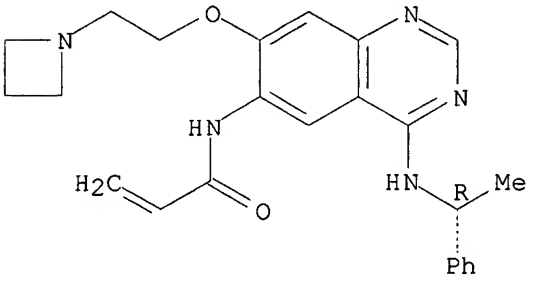
AB Title compds. [I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH2, PhCH2CH2; Rc = (substituted) cycloalkoxy, cycloalkylalkoxy; A = (alkyl-substituted) imino; B = CO, SO2; C = (substituted) allenylene, vinylene, butadienylene, ethynylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, carbonyloxyalkylene, carbonyliminoalkylene, bond, etc.; E = amino, (substituted) alkylamino, dialkylamino, etc.], were prepd. Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propoxy]quinazoline (prepn. given) in CH2Cl2 contg. Et3N at -10.degree. was treated with acryloyl chloride in THF to give 35% 4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation of F/L HERC cells with IC50 = <0.35 nM.

IT **314771-22-7P 314771-23-8P 314771-39-6P**
314771-40-9P 314771-41-0P 314771-42-1P
314771-43-2P 314771-44-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors)

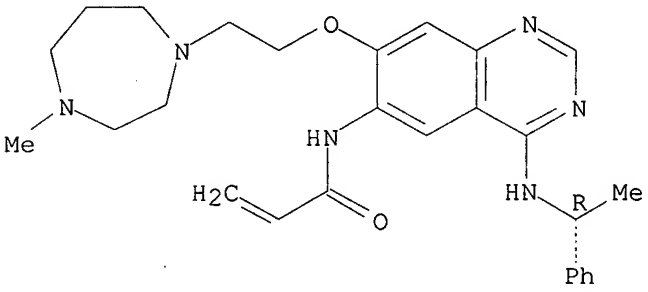
RN 314771-22-7 HCAPLUS
CN 2-Propenamide, N-[7-[2-(1-azetidinyl)ethoxy]-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



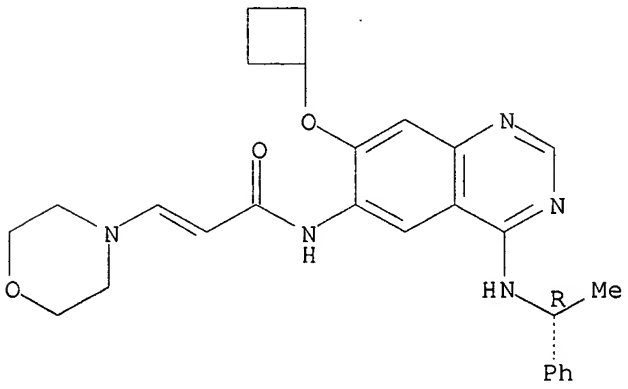
RN 314771-23-8 HCAPLUS
CN 2-Propenamide, N-[7-[2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)ethoxy]-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



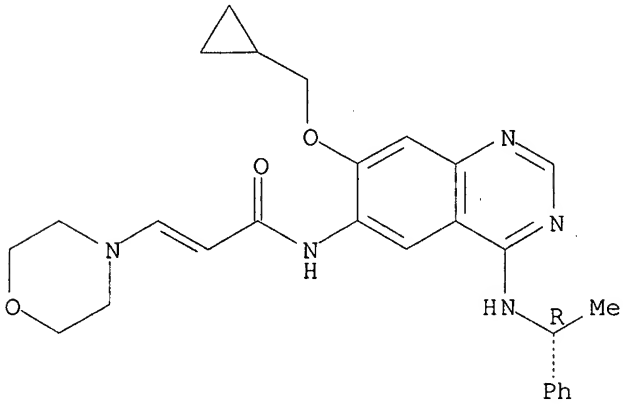
RN 314771-39-6 HCAPLUS
CN 2-Propenamide, N-[7-(cyclobutyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



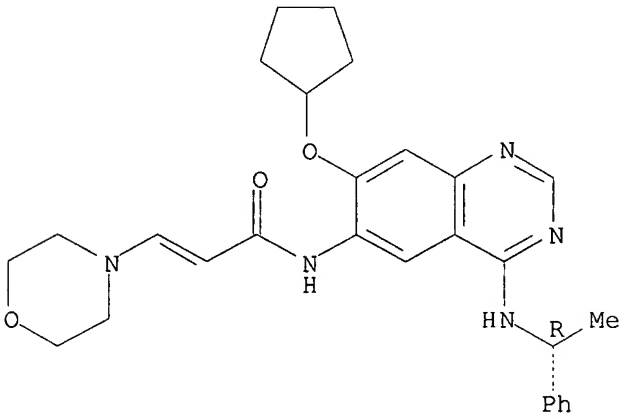
RN 314771-40-9 HCAPLUS
CN 2-Propenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



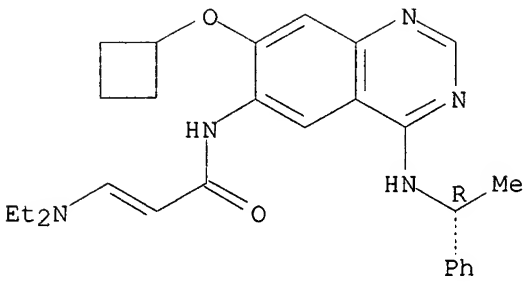
RN 314771-41-0 HCAPLUS
CN 2-Propenamide, N-[7-(cyclopentyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



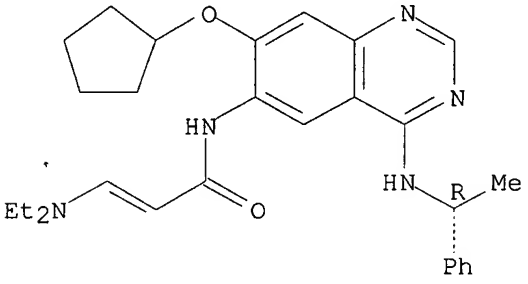
RN 314771-42-1 HCAPLUS
CN 2-Propenamide, N-[7-(cyclobutyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(diethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



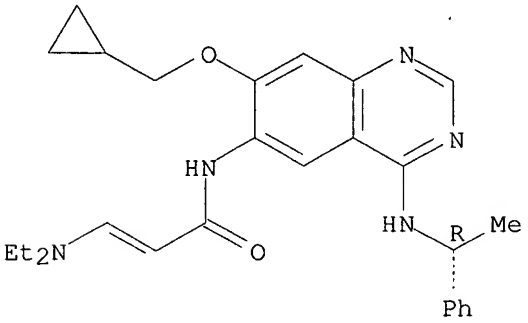
RN 314771-43-2 HCAPLUS
CN 2-Propenamide, N-[7-(cyclopentyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(diethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 314771-44-3 HCAPLUS
CN 2-Propenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(diethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:628125 HCAPLUS
DOCUMENT NUMBER: 133:207919
TITLE: Preparation of 4-amino-quinazoline and quinoline derivatives having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract

diseases

INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas; Solca, Flavio; Blech, Stefan

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany

SOURCE: PCT Int. Appl., 232 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

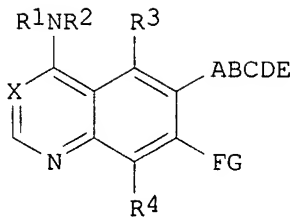
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051991	A1	20000908	WO 2000-EP1496	20000224
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19908567	A1	20000831	DE 1999-19908567	19990227
DE 19911366	A1	20000921	DE 1999-19911366	19990315
DE 19928306	A1	20001228	DE 1999-19928306	19990621
DE 19954816	A1	20010517	DE 1999-19954816	19991113
EP 1157011	A1	20011128	EP 2000-910695	20000224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008524	A	20011218	BR 2000-8524	20000224
NO 2001004114	A	20011015	NO 2001-4114	20010824

PRIORITY APPLN. INFO.:

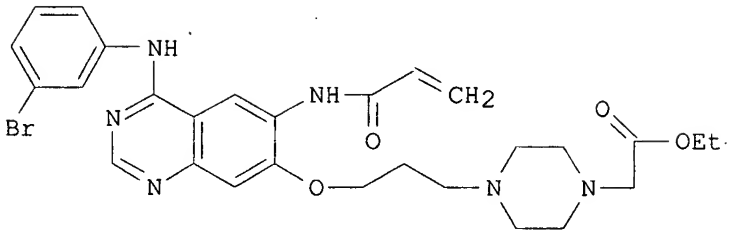
DE 1999-19908567	A	19990227
DE 1999-19911366	A	19990315
DE 1999-19928306	A	19990621
US 1999-149329P	P	19990817
DE 1999-19954816	A	19991113
WO 2000-EP1496	W	20000224

OTHER SOURCE(S): MARPAT 133:207919

GI



I



II

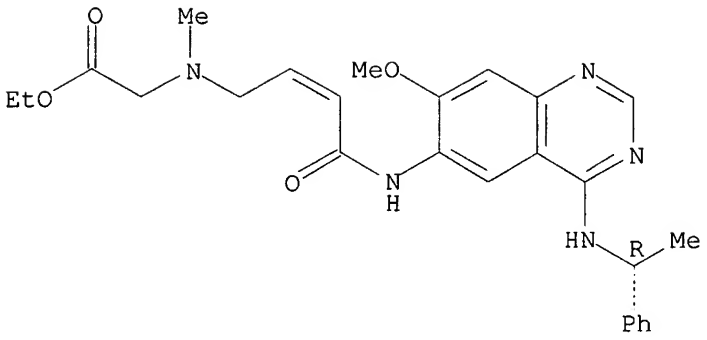
AB Title compds. [I; R1 = H, C1-C4-alkyl; R2 = (un)substituted Ph, benzyl, 1-phenylethyl; R3, R4 independently = H, F, Cl, CH3O, CH3OCH2, (CH3)2NCH2, (CH3CH2)2NCH2, pyrrolidino, piperidino, morpholino; X = C(CN), N; A = O, NH, (C1-C4)-alkylN; B = CO, SO2; C = 1,3-allenylene, 1,1-vinylene, 1,2-vinylene, 1,3-butadien-1,4-ylene, with CH3, CF3 substitution; D = alkylene, CO-alkylene, SO2-alkylene; CO, SO2; E = HOCO(CH2)nNR5, (HO)2P(:O)(CH2)nNR5; n = 1-6; R5 = H, alkyl], tautomers, stereoisomers, and physiol. acceptable salts are prepd. and having valuable pharmacol. properties, particularly an inhibiting effect on signal transduction mediated by tyrosine kinases. Title compds. are useful for treating tumoral diseases, diseases of the lungs and respiratory tract. Thus, the title compd. II was prepd. and tested by Cell Titer 96TM Aq. Nonradioactive Cell Proliferation Assay.

IT **290301-88-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases)

RN 290301-88-1 HCAPLUS

CN Glycine, N-[4-[[7-methoxy-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME)

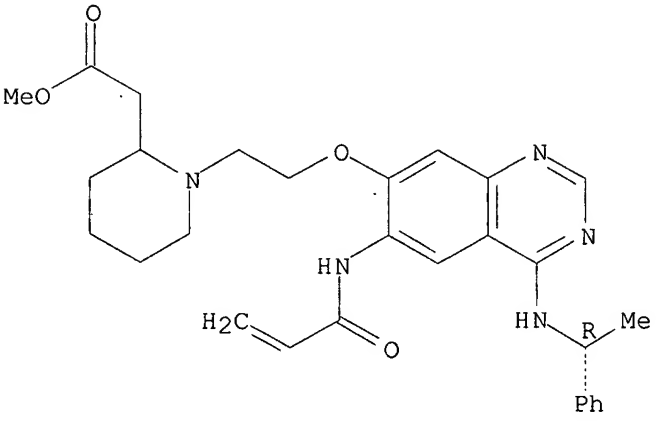
Absolute stereochemistry.
Double bond geometry unknown.



IT **290301-67-6P 290301-68-7P 290301-69-8P**
290301-70-1P 290301-71-2P 290301-72-3P
290302-75-9P 290302-77-1P 290302-79-3P
290302-85-1P 290302-87-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases)

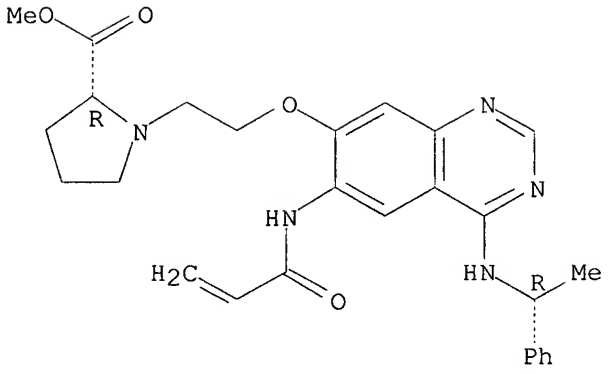
RN 290301-67-6 HCAPLUS
CN 2-Piperidineacetic acid, 1-[2-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



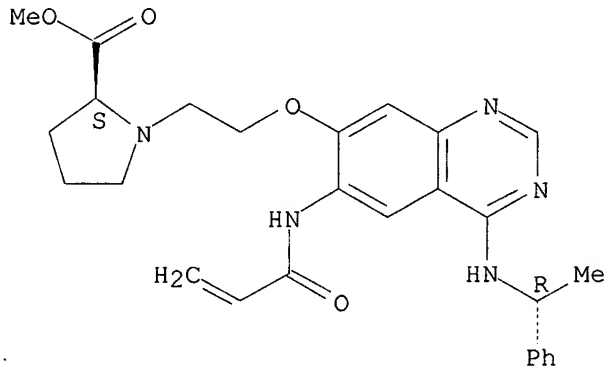
RN 290301-68-7 HCAPLUS
CN D-Proline, 1-[2-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



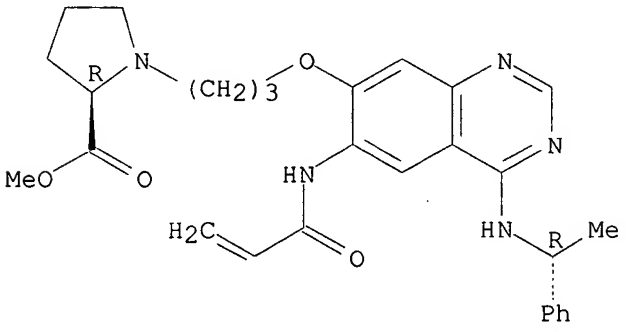
RN 290301-69-8 HCAPLUS
CN L-Proline, 1-[2-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



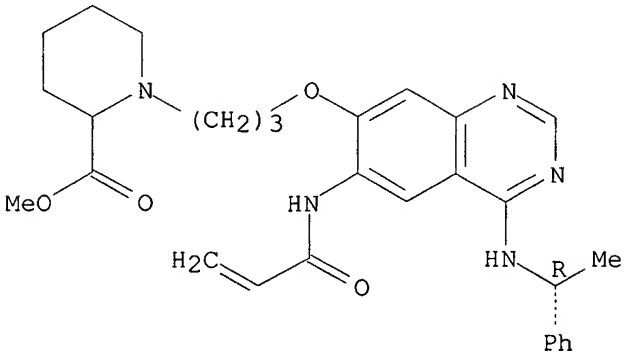
RN 290301-70-1 HCAPLUS
CN D-Proline, 1-[3-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]propyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



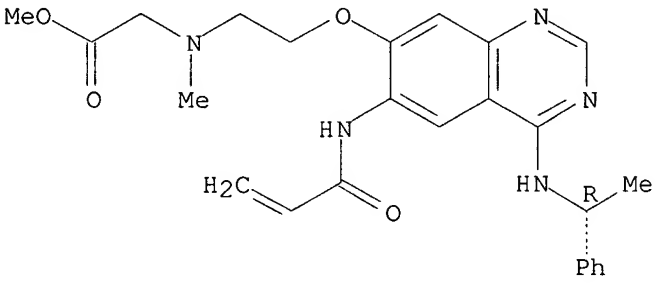
RN 290301-71-2 HCAPLUS
CN 2-Piperidinecarboxylic acid, 1-[3-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]propyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



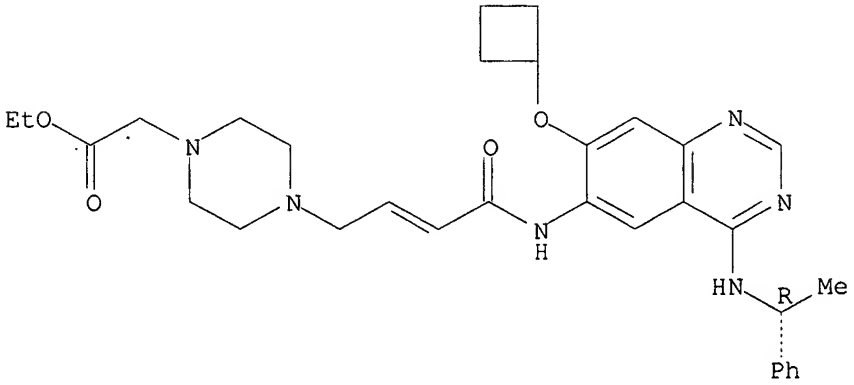
RN 290301-72-3 HCAPLUS
CN Glycine, N-methyl-N-[2-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 290302-75-9 HCAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[7-(cyclobutyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

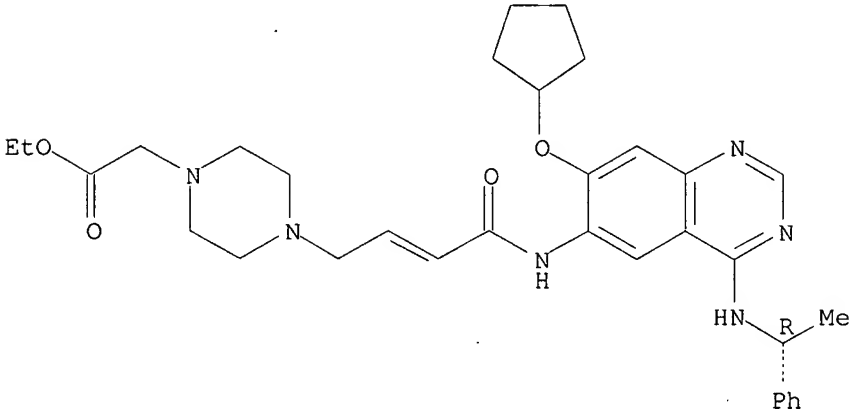
Absolute stereochemistry.
Double bond geometry unknown.



RN 290302-77-1 HCAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[7-(cyclopentyloxy)-4-[[(1R)-1-

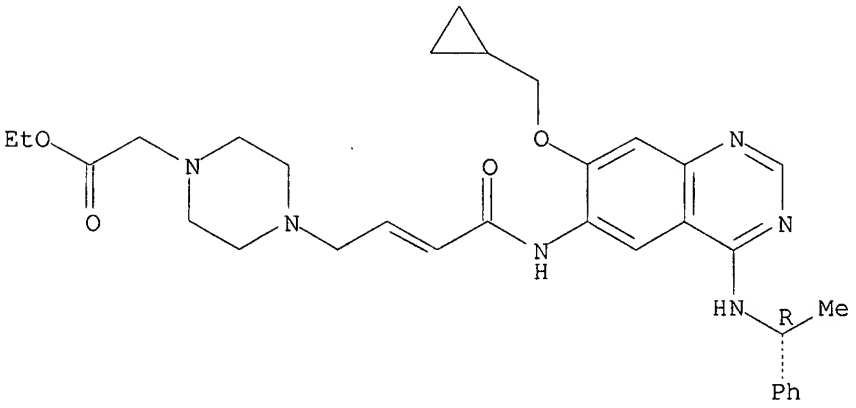
phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



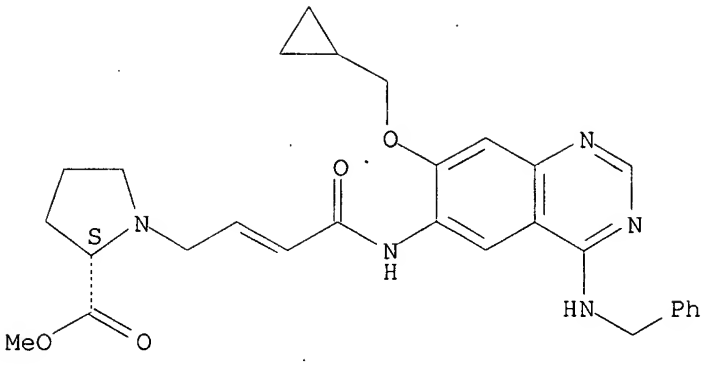
RN 290302-79-3 HCAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

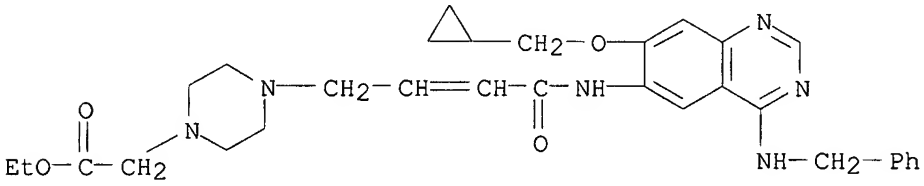


RN 290302-85-1 HCAPLUS
CN L-Proline, 1-[4-[[7-(cyclopropylmethoxy)-4-[(phenylmethyl)amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 290302-87-3 HCAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[7-(cyclopropylmethoxy)-4-[(phenylmethyl)amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

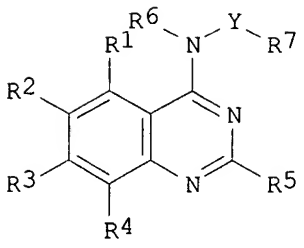


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:220729 HCAPLUS
DOCUMENT NUMBER: 132:251161
TITLE: Preparation of 4-aminoquinazolines for treating a patient having a precancerous lesions
INVENTOR(S): Pamukcu, Rifat; Piazza, Gary
PATENT ASSIGNEE(S): Cell Pathways, Inc., USA
SOURCE: U.S., 54 pp., Cont. of U.S. Ser. No. 475,197, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6046206	A	20000404	US 1997-846593	19970430
PRIORITY APPLN. INFO.:			US 1995-475197	19950607

OTHER SOURCE(S): MARPAT 132:251161
GI



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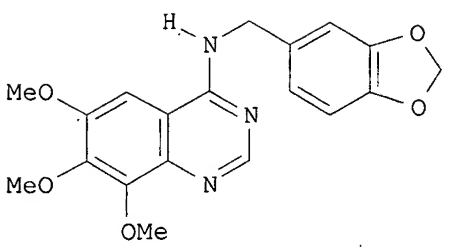


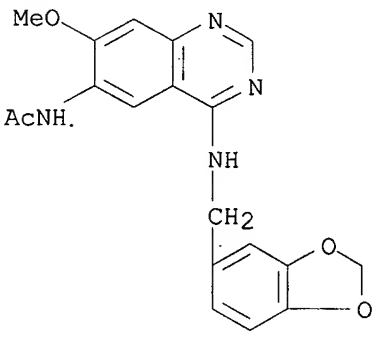
II

AB The title compds. [I; R1-R4 = H, alkoxy, hydroxyalkyl, etc.; R5 = H, halo, OH, etc.; R6 = H, alkyl, acyl, etc.; R7 = H, OH, CN, etc.; Y = (un)substituted (CH2)q (q = 1-8), CO], useful for the treatment of patients having precancerous lesions, and also for inhibiting the growth of neoplastic cells (no data), were prepd. Thus, reacting 4-chloro-6,7,8-trimethoxyquinazoline with piperonylamine in the presence of Na2CO3 in iso-PrOH afforded 69% II.

IT **150450-69-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 4-aminoquinazolines for treating a patient having a precancerous lesions)

RN 150450-69-4 HCAPLUS

CN Acetamide, N-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-7-methoxy-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:603427 HCAPLUS

DOCUMENT NUMBER: 119:203427

TITLE: Preparation of N-containing heterocyclic compounds as phosphodiesterase inhibitors.

INVENTOR(S): Takase, Yasutaka; Watanabe, Nobuhisa; Matsui, Makoto; Ikuta, Hironori; Kimura, Teiji; Saeki, Takao; Adachi, Hideyuki; Tokumura, Tadakazu; Mochida, Hisatoshi; et al.

PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan

SOURCE: PCT Int. Appl., 362 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

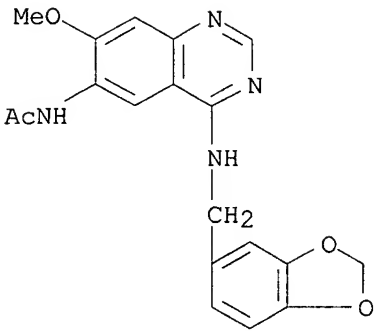
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9307124	A1	19930415	WO 1992-JP1258	19920930
W: AU, CA, FI, HU, JP, KR, NO, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
ZA 9207465	A	19930413	ZA 1992-7465	19920929
CN 1071164	A	19930421	CN 1992-110792	19920929
AU 9226851	A1	19930503	AU 1992-26851	19920930
AU 668363	B2	19960502		
EP 607439	A1	19940727	EP 1992-920913	19920930
EP 607439	B1	20020109		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
HU 70854	A2	19951128	HU 1994-910	19920930
JP 2000264877	A2	20000926	JP 2000-70130	19920930
JP 2000264885	A2	20000926	JP 2000-70142	19920930
JP 2000273089	A2	20001003	JP 2000-70138	19920930
AT 211734	E	20020115	AT 1992-920913	19920930
US 5576322	A	19961119	US 1994-196110	19940218
FI 9401417	A	19940325	FI 1994-1417	19940325
NO 9401101	A	19940530	NO 1994-1101	19940325
US 5693652	A	19971202	US 1995-408867	19950323
JP 10095776	A2	19980414	JP 1997-195696	19970722
JP 3081172	B2	20000828		
US 5801180	A	19980901	US 1997-904260	19970731

PRIORITY APPLN. INFO.:		
JP 1991-320853	A	19910930
JP 1993-506780	A3	19920930
JP 1997-195696	A3	19920930
WO 1992-JP1258	A	19920930
US 1994-196110	A3	19940218
US 1995-408867	A3	19950323

OTHER SOURCE(S): MARPAT 119:203427
GI For diagram(s), see printed CA Issue.
AB The title compds. [I; R1-R4 = H, halo, (halo)alkyl, (un)substituted cycloalkyl, alkoxy, etc.; R5 = H, OH, hydrazino, alkyl, (un)substituted cycloalkyl, alkoxy, etc.; R6 = H, halo, OH, cyano, alkyl, alkoxy, alkenyl, etc.; A = benzene ring, pyridine ring, cyclohexane ring; B = pyridine ring, pyrimidine ring, imidazole ring], useful for treatment of ischemia, heart attack, hypertension, cardiac insufficiency, and asthma (no data), are prepd. E.g., a mixt. of 4-hydroxy-6-carbamoylquinazoline, SOCl2, and POCl3 was reflexed for 20 h to give 4-chloro-6-cyanoquinazoline. 4-(4-Methoxybenzyl)amino-6,7,8-trimethoxyquinazoline (also prepd.) had an IC50 of 1.0 .mu.M against phosphodiesterase in an in vitro study.
IT **150450-69-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as phosphodiesterase inhibitor)
RN 150450-69-4 HCAPLUS
CN Acetamide, N-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-7-methoxy-6-quinazolinyl]- (9CI) (CA INDEX NAME)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=>

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L8                STR
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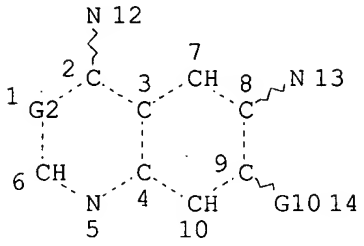


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  13

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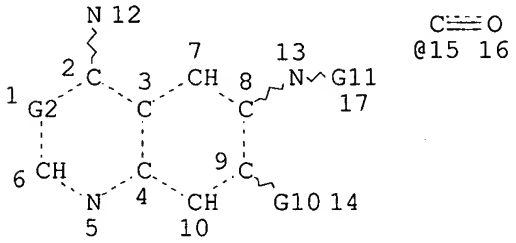


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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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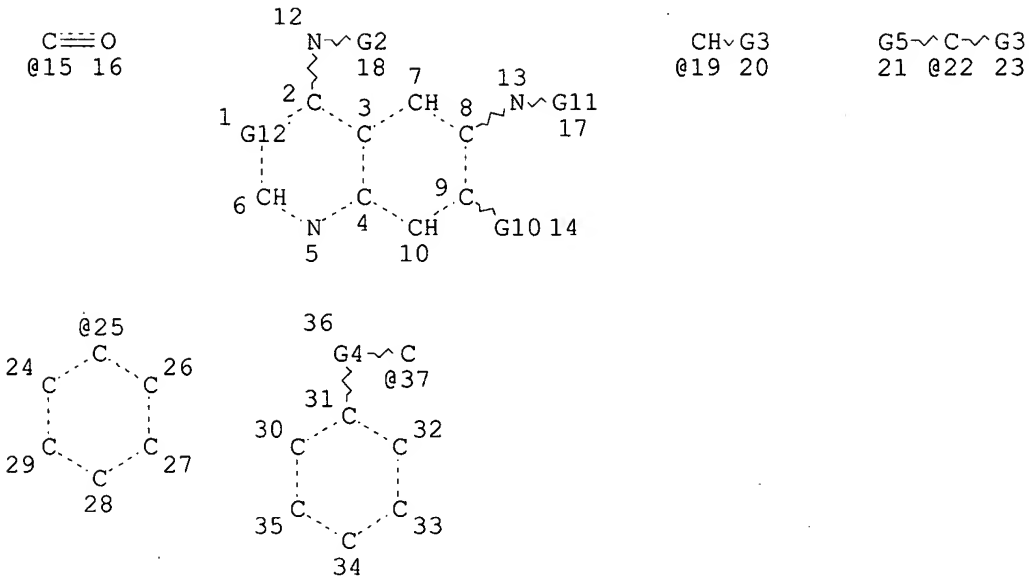

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VAR G11=15/S
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DEFAULT MLEVEL IS ATOM
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GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 36

STEREO ATTRIBUTES: NONE
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L18 39 SEA FILE=HCAPLUS ABB=ON PLU=ON L17 NOT L15

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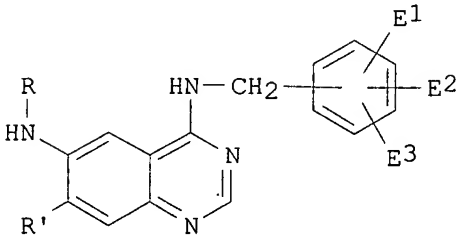
L18 ANSWER 1 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:610316 HCAPLUS
DOCUMENT NUMBER: 137:163829
TITLE: Use of a composition comprising a retinoid and an Erb inhibitor in the preparation of a medicament for the treatment of retinoid skin damage
INVENTOR(S): Elder, James Tilford; Varani, James
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: Eur. Pat. Appl., 43 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1230919	A2	20020814	EP 2002-2611	20020205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
AU 2002015470	A5	20020815	AU 2002-15470	20020207
JP 2002275095	A2	20020925	JP 2002-33608	20020212

PRIORITY APPLN. INFO.: US 2001-268220P P 20010212
OTHER SOURCE(S): MARPAT 137:163829
GI



I

AB Erb inhibitors used in combination with retinoids are effective to prevent skin injury otherwise caused by retinoids alone. A method of treating skin aging and similar skin disorders comprises administering retinoids in combination with erb inhibitors I (E1-E3 include halo; R is alkylcarbonyl or alkenylcarbonyl; R' is lower alkoxy optionally substituted with amino groups).

IT **198959-99-8 267243-28-7 289499-45-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(retinoid and Erb inhibitor for treatment of retinoid skin damage)

L18 ANSWER 2 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:353433 HCAPLUS
DOCUMENT NUMBER: 136:369616
TITLE: Preparation of 3-cyano-4-arylaminoquinolines as inhibitors of MAP kinase for use as antitumor agents
INVENTOR(S): Boyle, Francis Thomas; Gibson, Keith Hopkinson
PATENT ASSIGNEE(S): Astrazeneca A.B., Swed.; Astrazeneca UK Limited
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036570	A1	20020510	WO 2001-GB4733	20011025
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,				

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001095791 A5 20020515 AU 2001-95791 20011025

PRIORITY APPLN. INFO.: GB 2000-26745 A 20001102
GB 2000-26747 A 20001102
WO 2001-GB4733 W 20011025

OTHER SOURCE(S): MARPAT 136:369616.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. I [R1, R2, R3, R4 independently H, HO, halogen, NC, O2N, F3C, (un)substituted C1-C3 alkyl, (un)substituted amino, satd. heterocyclyl contg. two heteroatoms; R5 = NC, F, Cl, Br; R6 = divalent C1-C5 alkenyl, C3-C7 cycloalkyl, or heteroaryl moiety; R7 = AR8; A = bond, O, CO, S, SO, SO2, (un)substituted aminocarbonyl, (un)substituted carbonylamino, (un)substituted sulfonylamino, (un)substituted aminosulfonyl, (un)substituted amino; R8 = C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl; R9 = (un)substituted C3-C7 divalent cycloalkyl; R10 = (un)substituted arylene, heteroarylene, heteroarylene N-oxide, C3-C10 cycloalkylene; X = amino, (C1-C6)alkylamino, O, S, CH2; Y = amino, (C1-C6)alkylamino, O, S; Z = (un)substituted alkyl, alkylene, alkynylene, O, CO, COO, S, SO, SO2, (un)substituted aminocarbonyl, carbonylamino, sulfonylamino, aminosulfonyl, amino; n = 0,1; m and p independently 0-3; alternatively, R10Z(CH2)pR6R7 can be replaced with a heteroaryl or heterocyclyl-2,3-fused Ph ring] were prepd. as inhibitors of MAP kinase for use as antitumor agents. E.g., 1-fluoro-4-nitrobenzene undergoes nucleophilic substitution with (2-hydroxyphenoxy)acetic acid followed by coupling of the acid with Me glycinate, redn. of the nitro group with Pd/C, and reaction of the ester with N-methylpiperazine to give the aminophenoxymethylcarbonylaminoa cetyl piperazine II. E.g., coupling of II with 4-chloro-6,7-dimethoxy-3-quinolinenitrile gave the example compd. III. Biol. data was obtained for selected compds. Selected compds. inhibited MAP kinase with IC50 < 0.5 .mu.M; for example, III gave an IC50 of 3.8 nM. In addn., selected compds. inhibited the proliferation of human colon cancer cells with IC50 < 30 .mu.M; for example, III gave an IC50 of 1 .mu.M.

IT **423179-97-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(example compds.; prepn. of 4-arylamino-3-cyanoquinolines as inhibitors of MAP kinase for potential use as antitumor agents)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:171892 HCAPLUS
DOCUMENT NUMBER: 136:216762
TITLE: Preparation of 4-amino-6-heterocyclylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018376	A1	20020307	WO 2001-EP9536	20010818
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10042062	A1	20020307	DE 2000-10042062	20000826
AU 2001095482	A5	20020313	AU 2001-95482	20010818
US 2002115675	A1	20020822	US 2001-934631	20010822

PRIORITY APPLN. INFO.: DE 2000-10042062 A 20000826
US 2000-230542P P 20000905
WO 2001-EP9536 W 20010818

OTHER SOURCE(S): MARPAT 136:216762

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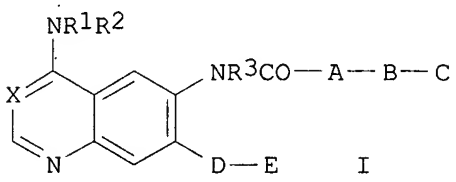


I

AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH2, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = (substituted) alkenyl, alkenylcarbonyl, etc.; C = (substituted) 2-oxomorpholin-4-yl, etc; D = oxyalkenyl, O; E = (substituted) amino, alkenylimino, imidazolyl, cycloalkyl; or DE = H, (substituted) alkoxy, etc.], were prepd. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[N-(ethoxycarbonylmethyl)-N-((R)-2-hydroxy-3-methoxypropyl)amino]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline (prepn. given) and MeSO2OH in MeCN were stirred for 4 h under reflux to give 69% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[(R)-2-methoxymethyl-6-oxomorpholin-4-yl]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 2 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402569-98-6P 402569-99-7P 402570-00-7P**
402570-01-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

IT **402569-87-3P 402569-89-5P 402569-90-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 39 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:86818 HCAPLUS
DOCUMENT NUMBER: 136:395481
TITLE: Differential sensitivity of cancer cells to inhibitors of the epidermal growth factor receptor family
AUTHOR(S): Bishop, Philippe C.; Myers, Timothy; Robey, Robert; Fry, David W.; Liu, Edison T.; Blagosklonny, Mikhail V.; Bates, Susan E.
CORPORATE SOURCE: Medicine Branch, NCI, NIH, Bethesda, MD, 20892, USA
SOURCE: Oncogene (2002), 21(1), 119-127
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clin. responses to the HER1 (EGF receptor) inhibitors and HER2/neu/ErbB2 inhibitors correlate with high levels of receptor expression. However, a significant subset of patients with high receptor levels appear to be refractory to treatment. We have obsd. similar results in the 60 cell lines of the NC1 Anti-Cancer Drug Screen using a panel of 11 selective HER1 inhibitors. As expected, low HER1-expressing cell lines were insensitive to HER1 inhibitors. In cell lines with high HER1 expression, low concns. of HER1 inhibitors potently inhibit both HER1 phosphorylation and the mitogen-activated protein kinase (MAPK) pathway. However, this inhibition did not always correlate with cellular arrest. High HER1-expressing cell lines can be subdivided into two groups based on their sensitivity to HER1 inhibitors. In the sensitive group, receptor and growth inhibition was concordant and occurred at submicromolar concns. of HER1 inhibitors. In the insensitive group, receptor inhibition occurred at a low concn. (< 1 M) but concns. that were ten times or higher were required for growth inhibition. Also, neither induction of p21 and cyclin D1 nor p53 status could explain the difference between sensitive and insensitive cells. Although EGF activated the MAPK pathway in all cell lines, only drug-sensitive cell lines responded to EGF (accelerated entry from G1 to S) and to HER1 inhibitors (G1 arrest) by changes in cell cycling. Furthermore, an EGF-dependent immortalized mammary epithelial cell line was extremely sensitive to a panel of HER1 inhibitors. We infer that independence from mitogen-mediated signaling confers insensitivity to HER1 inhibitors in a large subset of cancer cell lines.

IT **289499-45-2**, NSC 709239
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PD 183805; sensitivity of cancer cells to inhibitors of EGF receptor family)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:74864 HCAPLUS
DOCUMENT NUMBER: 137:134227
TITLE: Epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy
AUTHOR(S): Adjei, Alex A.
CORPORATE SOURCE: Division of Medical Oncology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA
SOURCE: Drugs of the Future (2001), 26(11), 1087-1092
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Receptor tyrosine kinases are transmembrane proteins involved in signal transduction. They propagate growth factor signals from the cell surface to intracellular processes that control crit. functions such as growth, differentiation, angiogenesis and inhibition of apoptosis. In malignancies, these signaling pathways are often exploited to optimize

tumor growth and metastasis. One such family of receptor tyrosine kinases is the epidermal growth factor receptor (EGFR) tyrosine kinase. These receptors are overexpressed in a wide variety of epithelial cancers and have been implicated in tumor aggressiveness. Thus, targeting the EGFR tyrosine kinase has attracted considerable attention. This review will summarize current preclin. and clin. knowledge of the small-mol. oral inhibitors of the EGFR tyrosine kinase, which include ZD-1839, OSI-774, CI-1033, EKB-569, PKI-166, GW-2016 and BIBX-1382.

IT **257933-82-7**, EKB 569 **289499-45-2**, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:10449 HCAPLUS
DOCUMENT NUMBER: 136:74658
TITLE: Polymorphic forms/hydrates of N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)-quinazolin-6-yl]acrylamide dihydrochloride
INVENTOR(S): Barth, Hubert; Steiner, Klaus; Schneider, Simon; Huels, Dietmar; Muehlenfeld, Andreas; Westermayer, Manfred
PATENT ASSIGNEE(S): Goedecke G.m.b.H., Germany
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000630	A1	20020103	WO 2001-EP6733	20010615
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10031971	A1	20020110	DE 2000-10031971	20000630

PRIORITY APPLN. INFO.: DE 2000-10031971 A 20000630

AB Polymorphic forms/hydrates of N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)quinazolin-6-yl]acrylamide-2HCl (I), processes for their prepn., as well as their use for the prepn. of pharmaceuticals with irreversible tyrosine kinase inhibiting action are described. N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)quinazolin-6-yl]acrylamide was dissolved in EtOH and treated with HCl to give I monohydrate (Form M). The compd. was thermally stable when subjected to different thermal stress conditions.

IT **289499-45-2P 383908-86-9P 383908-87-0P 383908-88-1P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polymorphic forms/hydrates of (chlorofluorophenylamino)morpholinylpropoxyquinazolinylacrylamide)

IT **267243-28-7**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)

(prepn. of polymorphic forms/hydrates of (chlorofluorophenylamino)morph olinylpropoxyquinazolinylacrylamide)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:935435 HCAPLUS
DOCUMENT NUMBER: 136:84677
TITLE: Methods for enhancing antibody-induced cell lysis and treating cancer
INVENTOR(S): Weiner, George; Hartmann, Gunther
PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
SOURCE: PCT Int. Appl., 312 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097843	A2	20011227	WO 2001-US20154	20010622

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-213346P P 20000622
AB The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.
IT **289499-45-2**, PD 183805
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunostimulatory nucleic acids and antibody specific to CD20, CD22, CD19 or CD40 for inducing cell lysis and treating cancer)

L18 ANSWER 8 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:921399 HCAPLUS
DOCUMENT NUMBER: 137:72358
TITLE: CI-1033, a pan-erbB tyrosine kinase inhibitor
AUTHOR(S): Slichenmyer, William J.; Elliott, William L.; Fry, David W.
CORPORATE SOURCE: Department of Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Seminars in Oncology (2001), 28(5, Suppl. 16), 80-85
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Overexpression of the erbB family of receptor tyrosine kinases has been implicated in a variety of tumors including breast, lung, prostate, and brain. Most solid tumors express one or more of these receptors, which can often be related to tumor aggressiveness and poor patient prognosis. CI-1033, a pan-erbB tyrosine kinase inhibitor, is a clin. promising agent that is active against all four members of the erbB receptor tyrosine kinase family. In vitro studies of human cancer cell lines indicate that CI-1033 results in prompt, potent, and sustained inhibition of tyrosine kinase activity. This inhibition is highly

selective for erbBI (epidermal growth factor receptor), erbB2, erbB3, and erbB4 without inhibiting tyrosine kinase activity of receptors such as platelet-derived growth factor receptor, fibroblast growth factor receptor, and insulin receptor, even at high concns. Treatment of athymic nude mice bearing xenografts of human A431 epidermoid carcinoma, H125 non-small cell lung carcinoma, and SF-767 glioblastoma results in highly significant suppression of tumor growth. The major toxicity in animals is diarrhea, which is more severe at higher doses. In animal models, all side effects are reversible on cessation of treatment. Thus, CI-1033, which is currently undergoing phase I clin. trials, holds significant potential for use in a broad range of solid tumors.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI-1033, a pan-erbB tyrosine kinase inhibitor)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:921398 HCAPLUS
DOCUMENT NUMBER: 137:87979
TITLE: Anticancer therapy targeting the ErbB family of receptor tyrosine kinases
AUTHOR(S): Slichenmyer, William J.; Fry, David W.
CORPORATE SOURCE: Departments of Oncology Clinical Development and Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Seminars in Oncology (2001), 28(5, Suppl. 16), 67-79
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several agents that target one or more members of the erbB family of receptor tyrosine kinases are currently undergoing clin. investigation. The monoclonal antibody trastuzumab has been shown effective in erbB2-expressing metastatic breast cancer when administered as a single agent or in combination with cytotoxic chemotherapy. Toxicities assocd. with trastuzumab include infusion-related fever and chills, hypersensitivity reactions, and congestive heart failure. C225 is a monoclonal antibody directed against the epidermal growth factor receptor, which has shown encouraging antitumor activity in early clin. development. The orally active tyrosine kinase inhibitors show encouraging antitumor activity in preclin. models and early clin. trials. Members of this class currently in clin. development include ZD1839, OSI774, and CI-1033. Evidence to data suggests that the major role for erbB receptor-targeting drugs will be in combined therapy to enhance response to cytotoxic drugs, and in long-term monotherapy to maintain response and prevent disease progression or recurrence.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer therapy targeting the ErbB family of receptor tyrosine kinases)

REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:800795 HCAPLUS
DOCUMENT NUMBER: 136:95729
TITLE: Evidence for epidermal growth factor receptor-enhanced chemosensitivity in combinations of cisplatin and the new irreversible tyrosine kinase inhibitor CI-1033

AUTHOR(S): Gieseg, Michael A.; De Bock, Charles; Ferguson, Lynnette R.; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical & Health Sciences, The University of Auckland, Auckland, 1000, N. Z.
SOURCE: Anti-Cancer Drugs (2001), 12(8), 683-690
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Irreversible inhibitors of the epidermal growth factor receptor (EGFR) are showing promise in clin. trials. This report is the first to show that inhibition of the EGFR tyrosine kinase by an irreversible binder synergizes with cisplatin, at least in EGFR-overexpressing tissue culture cell lines in vitro. Unlike previous synergies demonstrated between ErbB2 blockade and DNA-damaging drugs, the synergy between the irreversible EGFR inhibitor and cisplatin does not appear to involve the repair of DNA-cisplatin adducts. Given the current clin. data, this combination may be of more than theor. interest.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evidence for EGFR-enhanced chemosensitivity in combinations of cisplatin and CI-1033)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:799778 HCAPLUS
DOCUMENT NUMBER: 136:112324
TITLE: Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation
AUTHOR(S): Dowlati, Afshin; Haaga, John; Remick, Scot C.; Spiro, Timothy P.; Gerson, Stanton L.; Liu, Lili; Berger, Sosamma J.; Berger, Nathan A.; Willson, James K. V.
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine and Developmental Therapeutics Program, Ireland Cancer Center at University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH, 44106, USA
SOURCE: Clinical Cancer Research (2001), 7(10), 2971-2976
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the setting of target-based anticancer drug development, it is crit. to establish that the obsd. preclin. activity can be attributed to modulation of the intended target in early phase trials in human subjects. This paradigm of target modulation allows the authors to det. a Phase II or III dose (optimal biochem./biol. modulatory dose) that may not necessarily be the max. tolerated dose. A major obstacle to target-based (often cytostatic) drug development has been obtaining relevant tumor tissue during clin. trials of these novel agents for lab. anal. of the putative marker of drug effect. From 1989 to present, the authors have completed seven clin. trials in which the end point was a biochem. or biol. modulatory dose in human tumor tissues (not surrogate tissue). Eligibility enrollment required that patients have a biopsiable lesion either with computerized tomog. (CT) guidance or direct visualization and consent to sequential (pre and posttreatment) biopsies. A total of 192 biopsies were performed in 107 patients. All but 8 patients had sequential pre and posttreatment biopsies. Seventy-eight (73%) of the 107 patients had liver lesion biopsies. In eight patients, either one or both

biopsies contained insufficient viable tumor tissue or no tumor tissue at all for anal. Of a total of 99 patients in whom the authors attempted to obtain paired biopsies, a total of 87 (88%) were successful. Reasons for failure included patient refusal for a second biopsy (n = 2), vasovagal reaction with first biopsy precluding a second biopsy (n = 1), subcapsular hepatic bleeding (n = 1), and most commonly obtaining necrotic tumor, fibrous, or normal tissue in one of the two sequential biopsies (n = 8). This is the first and largest reported series demonstrating that with adequate precautions and experience, sequential tumor biopsies are feasible and safe during early phase clin. trials.

IT **289499-45-2**, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sequential human tumor biopsies in early phase clin. trials of anticancer agents for pharmacodynamic evaluation)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 12 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:799777 HCAPLUS
DOCUMENT NUMBER: 137:27578
TITLE: A novel approach in the treatment of cancer: Targeting the epidermal growth factor receptor
AUTHOR(S): Ciardiello, Fortunato; Tortora, Giampaolo
CORPORATE SOURCE: Cattedra di Oncologia Medica. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli "Federico II,", Naples, 80131, Italy
SOURCE: Clinical Cancer Research (2001), 7(10), 2958-2970
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a no. of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The crit. role the EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclin. studies and the early clin. trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to cancer therapy. A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clin. development include monoclonal antibodies to prevent ligand binding and small mol. inhibitors of the tyrosine kinase enzymic activity to inhibit autophosphorylation and downstream intracellular signaling. At least five blocking monoclonal antibodies have been developed against the EGFR. Among these, IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody that has been the first anti-EGFR targeted therapy to enter clin. evaluation in cancer patients in Phase II and III studies, alone or in combination with conventional therapies, such as radiotherapy and chemotherapy. A no. of small mol. inhibitors of the EGFR tyrosine kinase enzymic activity is also in development. OSI-774 and ZD1839 (Iressa) are currently in Phase II and III development, resp. ZD1839, a p.o. active, selective quinazoline deriv. has demonstrated promising in vitro and in vivo antitumor activity. Preliminary results from Phase I and II trials in patients with advanced disease demonstrate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clin. efficacy in patients with a variety of tumor types. This mini-review describes the EGFR inhibitors in clin. development.

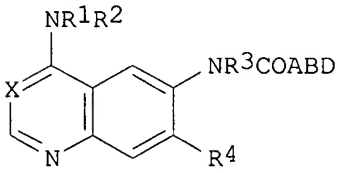
IT **289499-45-2**, PD183805
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting the epidermal growth factor receptor as a novel approach in

the treatment of cancer)
REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 13 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:762992 HCAPLUS
DOCUMENT NUMBER: 135:303907
TITLE: Preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction.
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10017539	A1	20011011	DE 2000-10017539	20000408
DE 10040525	A1	20020228	DE 2000-10040525	20000818

PRIORITY APPLN. INFO.: DE 2000-10017539 A 20000408
DE 2000-10040525 A 20000818
OTHER SOURCE(S): MARPAT 135:303907
GI



I

AB Title compds. [I; X = NCN, N; R1 = H, alkyl; R2 = (substituted) Ph, PhCH2, PhCH2CH2; R3 = H, alkyl; R4 = H, alkoxy, cycloalkoxy, cycloalkylalkoxy; A = (substituted) vinylene; B = bond, (fluoro)alkylene; D = substituted pyrrolidinyl, piperidinyl, piperazinyl, etc.], were prepd. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(piperazin-1-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline (prepn. given) in THF was treated with Et3N and then with 3-bromodihydrofuran-2-one in THF under ice cooling followed by stirring for 48 h at room temp. to give 56% 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[4-(2-oxotetrahydrofuran-3-yl)piperazin-1-yl]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.05 nM.
IT **365532-35-0P 365532-36-1P 365532-37-2P**

365532-39-4P 365532-40-7P 365532-41-8P
365532-42-9P 365532-44-1P 365532-45-2P
365532-46-3P 365532-47-4P 365532-48-5P
365532-49-6P 367282-07-3P 367282-12-0P
367282-15-3P 367282-23-3P 367282-25-5P
367282-27-7P 367282-29-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)

IT **367283-05-4 367283-07-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)

IT **290303-47-8P 290304-01-7P 365532-06-5P**
365532-07-6P 365532-18-9P 365532-19-0P
365532-31-6P 367282-36-8P 367282-44-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)

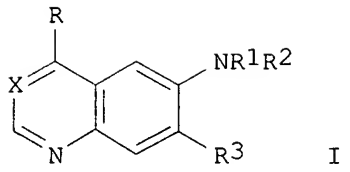
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 14 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:747043 HCAPLUS
DOCUMENT NUMBER: 135:303901
TITLE: Bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma KG, Germany
SOURCE: Ger. Offen., 28 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10017539	A1	20011011	DE 2000-10017539	20000408
US 2001044435	A1	20011122	US 2001-816003	20010323
WO 2001077104	A1	20011018	WO 2001-EP3694	20010331

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2000-10017539 A 20000408
DE 2000-10040525 A 20000818
OTHER SOURCE(S): MARPAT 135:303901
GI



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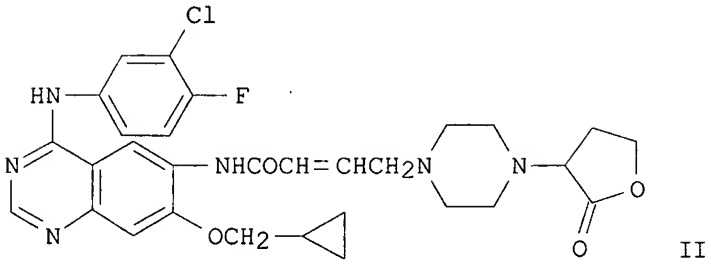

II

AB Bicyclic heterocycles I [X = N, CCN; R = substituted NH2; R1 = H, alkyl; R2 = acyl; R3 = H, (un)substituted alkoxy, cycloalkoxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy] were prepd. for use as inhibitors of tyrosine kinase-mediated signal transduction for treatment of tumors and diseases of the lung and airway. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-7-fluoro-6-nitroquinazoline was treated with cyclopropylmethanol, followed by redn. to the amine, reaction with 4-bromocrotonic acid and N-tert.-butoxycarbonylpiperazine, and deblocking to give the quinazoline II. II had an IC50 for inhibition of epidermal growth factor dependent proliferation of 0.05 nM.

IT **365532-35-0P 365532-39-4P 365532-42-9P**
365532-45-2P 365532-47-4P 365532-48-5P
365532-49-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

IT **290303-47-8P 290304-01-7P 365532-06-5P**
365532-07-6P 365532-10-1P 365532-18-9P
365532-19-0P 365532-21-4P 365532-31-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

IT **365532-36-1P 365532-37-2P 365532-38-3P**
365532-40-7P 365532-41-8P 365532-43-0P
365532-44-1P 365532-46-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

L18 ANSWER 15 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:730715 HCAPLUS
DOCUMENT NUMBER: 135:288636
TITLE: Synergistic methods and compositions for treating cancer using two or more anticancer agents
INVENTOR(S): Lee, Francis Y.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072721	A2	20011004	WO 2001-US9193	20010322
WO 2001072721	A3	20020613		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002002162	A1	20020103	US 2001-817456	20010326

PRIORITY APPLN. INFO.: US 2000-192278P P 20000327

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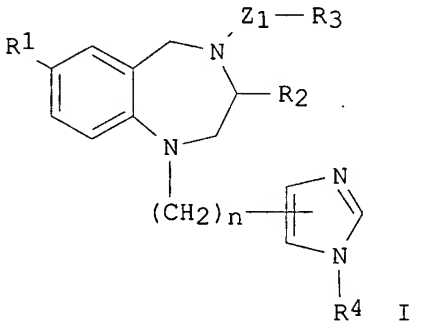

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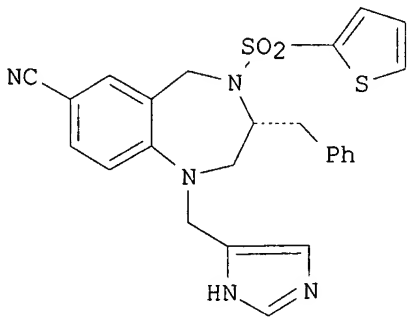


II

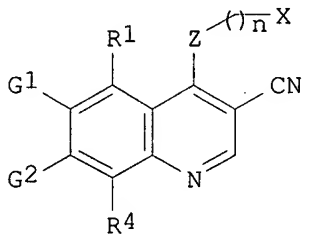
AB The present invention provides a synergistic method for the treatment of cancer which comprises administering a synergistically, therapeutically effective amt. of: (i) at least agent selected from the group consisting of cytotoxic agents and cytostatic agents, and (ii) a compd. of formula [I; R1 = Cl, Br, CN, substituted Ph, substituted pyridyl; R2 = alkyl, aralkyl; R3,R5 = substituted alkyl, aryl, heterocycle; R4 = H, alkyl; Z1 = CO, SO2, CO2, SO2N(R5); n = 1,2] or a pharmaceutically acceptable salt thereof. The present invention further provides a pharmaceutical compn. for the synergistic treatment of cancer which comprises at least one agent selected from the group consisting of antiproliferative cytotoxic agents and antiproliferative cytostatic agents, a compd. of formula I, and a pharmaceutically acceptable carrier. Synergism was obsd. when non-proliferating tumor cells were treated with diazepine II.cntdot.HCl and paclitaxel (III) simultaneously or when III preceded II.cntdot.HCl.

IT **257933-82-7**, EKB 569
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic methods using two or more anticancer agents for treating cancer)

L18 ANSWER 16 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:721437 HCAPLUS
DOCUMENT NUMBER: 135:272896
TITLE: Preparation of substituted 3-cyanoquinolines as protein tyrosine kinases inhibitors
INVENTOR(S): Wissner, Allan; Tsou, Hwei-ru; Berger, Dan M.; Floyd, Middleton B., Jr.; Hamann, Philip R.; Zhang, Nan; Frost, Philip
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: U.S., 57 pp., Cont. of U.S. Ser. No. 405,868, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6297258	B1	20011002	US 2000-630270	20000801

PRIORITY APPLN. INFO.: US 1998-150699P P 19980929
US 1999-405868 B1 19990924
OTHER SOURCE(S): MARPAT 135:272896
GI



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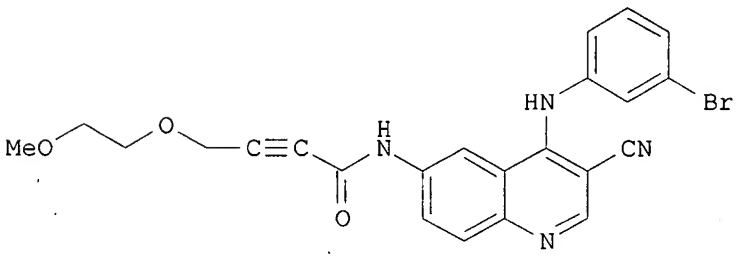


II

AB Title compds. I [X = cycloalkyl, pyridinyl, pyrimidinyl, etc.; Z = NH, O, S, NR; R = alkyl; G1, G2, R1, R4 = H, halo, alkyl, alkynyl, etc.; n = 0, 1], protein tyrosine kinase inhibitors, were prepd. Examples included 189 compds. and 6 bioassays. E.g., II was prepd. by coupling the 4-(2-methoxyethoxy)but-2-ynoic acid with 6-amino-3-cyano-4-[(3-bromophenyl)amino]quinoline (i-BuOCOCl, N-methylmorpholine, THF, 0.degree.C, 3 h) in 32% yield after purifn. II had IC50 = 0.006 .mu.M for EGFR kinase. I are useful as antineoplastic agents.

IT **263149-00-4P 263149-01-5P 263149-02-6P**
263149-03-7P 263149-04-8P 263149-06-0P
263149-07-1P 263149-08-2P 263149-13-9P
263149-14-0P 263149-16-2P 263149-17-3P

263149-18-4P 263149-19-5P 263149-20-8P
263149-26-4P 263149-30-0P 263149-44-6P
263149-45-7P 263149-46-8P 263149-47-9P
263149-90-2P 263150-04-5P 263150-31-8P
263150-32-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of cyanoquinolines as protein tyrosine kinase inhibitors)

IT **263149-21-9P 263149-22-0P 263149-23-1P**
263149-24-2P 263149-25-3P 263149-27-5P
263149-28-6P 263149-29-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of cyanoquinolines as protein tyrosine kinase inhibitors)

IT **263150-36-3P 263150-38-5P 263150-40-9P**
263150-42-1P 263150-44-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of cyanoquinolines as protein tyrosine kinase inhibitors)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 17 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:713163 HCAPLUS
DOCUMENT NUMBER: 135:267215
TITLE: Combined treatment with keratinocyte growth factor and epidermal growth factor receptor (EGFR) inhibitor for reducing EGFR inhibitor-associated epithelial toxicity
INVENTOR(S): Miller, Penelope Elizabeth; Moyer, James Dale
PATENT ASSIGNEE(S): Pfizer Products, Inc., USA; OSI Pharmaceuticals, Inc.
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070255	A2	20010927	WO 2001-US8207	20010315
WO 2001070255	A3	20020228		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002061304	A1	20020523	US 2001-808751	20010315

PRIORITY APPLN. INFO.: US 2000-190697P P 20000320

AB Compns. and methods are provided for treating the epithelial toxicity caused by administering to a human cancer patient an epidermal growth factor receptor (EGFR) inhibitor. The pharmaceutical compn. preferably comprises an EGFR inhibitor and a keratinocyte growth factor (KGF) in a pharmaceutically acceptable carrier. The method of treatment comprises co-administering to the patient a therapeutically effective amt. of KGF with the EGFR inhibitor.

IT **289499-45-2**, PD 183805
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(keratinocyte growth factor and epidermal growth factor receptor (EGFR) inhibitor combination treatment for reducing EGFR inhibitor-assocd. epithelial toxicity)

L18 ANSWER 18 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:693148 HCAPLUS
DOCUMENT NUMBER: 135:242152
TITLE: Preparation of 4-anilinoquinoline-3-carbonitriles as colonic polyp inhibitors
INVENTOR(S): Frost, Philip; Discafani-Marro, Carolyn M.
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: PCT Int. Appl., 207 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

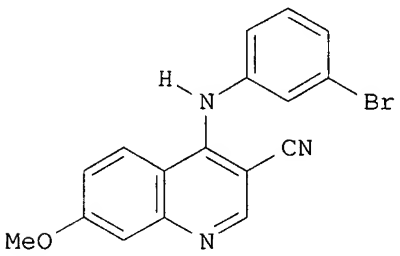
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068186	A2	20010920	WO 2001-US7068	20010306
WO 2001068186	A3	20020117		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6384051	B1	20020507	US 2001-805070	20010313

PRIORITY APPLN. INFO.:
US 2000-304198P P 20000313
US 2000-524196 A 20000313

OTHER SOURCE(S): MARPAT 135:242152
GI



II

AB R(CH2)nZZ1CN [I; R = (un)substituted cycloalkyl, -Ph, -pyridinyl, -pyrimidinyl; Z = O, S, (alkyl)imino; Z1 = 5-8-(un)substituted quinoline-4,3-diyl; n = 0 or 1] were prepd. Thus, 3-(MeO)C6H4NH2 was cyclocondensed with NCC(:CHOEt)CO2Et and the chlorinated product aminated by 3-BrC6H4NH2 to give title compd. II. Data for biol. activity of 1 prepd. I were given.

IT **214484-05-6P 214484-07-8P 214485-38-8P 214485-56-0P 214485-57-1P 214485-58-2P 214485-61-7P 214485-62-8P 214485-63-9P 214485-66-2P 214485-67-3P 214485-70-8P 214485-71-9P 214485-72-0P 214485-73-1P 214485-80-0P 214486-79-0P 214486-80-3P 326894-84-2P**

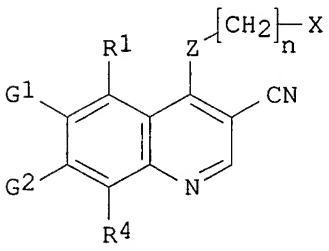
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 4-anilinoquinoline-3-carbonitriles as colonic polyp inhibitors)

IT **361162-96-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 4-anilinoquinoline-3-carbonitriles as colonic polyp inhibitors)

L18 ANSWER 19 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:672213 HCAPLUS
DOCUMENT NUMBER: 135:226901
TITLE: Preparation of 3-cyanoquinolines as protein tyrosine kinase inhibitors
INVENTOR(S): Wissner, Allan; Tsou, Hwei-ru; Berger, Dan M.; Floyd, Middleton B., Jr.; Hamann, Philip R.; Zhang, Nan; Salvati, Mark E.; Frost, Philip
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: U.S., 68 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6288082	B1	20010911	US 1999-406573	19990924

PRIORITY APPLN. INFO.: US 1998-150693P P 19980929
OTHER SOURCE(S): MARPAT 135:226901
GI



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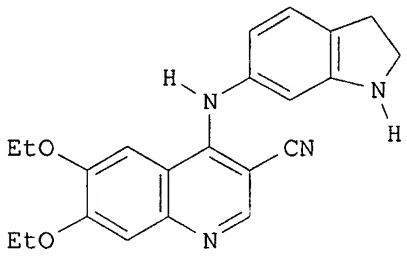


II

AB The title compds. [I; X = (un)substituted bicyclic aryl or bicyclic heteroaryl ring system of 8-12 atoms where the bicyclic heteroaryl ring contains 1-4 heteroatoms selected from N, O and S; Z = (un)substituted NH, O, S; G1, G2, R1, R4 = H, halo, alkyl, etc.; n = 0-1], useful as antineoplastic agents and in the treatment of polycystic kidney disease, were prepd. Thus, Me 2-amino-4,5-diethoxybenzoate was N-condensed with HCNMe2/POCl3 and the product cyclocondensed with MeCN to give, after POCl3 treatment, 4-chloro-6,7-diethoxyquinoline-3-carbonitrile which was aminated by 6-aminoindoline to give title compd II. Data for biol. activity (inhibition of EGFR kinase, KDR, Eck, Mek-Erk) of I were given.

IT **263170-75-8P 263170-78-1P 263170-81-6P**
263170-84-9P 263170-88-3P 263170-91-8P
263171-07-9P 263171-10-4P 263171-15-9P
263171-29-5P 263171-32-0P 263171-35-3P

263171-38-6P 263171-44-4P 263171-48-8P
263171-49-9P 263171-50-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-cyanoquinolines as protein tyrosine kinase inhibitors)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 20 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:516932 HCAPLUS
DOCUMENT NUMBER: 135:313144
TITLE: The 4-anilinoquinazoline class of inhibitors of the erbB family of receptor tyrosine kinases
AUTHOR(S): Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SOURCE: Farmaco (2001), 56(1-2), 51-56
CODEN: FRMCE8; ISSN: 0014-827X
PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The erbB family of receptor tyrosine kinase enzymes, and particularly EGFR and HER2/neu, have become important targets for potential anticancer drugs. The substrate protein binding site theor. is the more attractive intracellular target on these enzymes, possessing lower homol. than the ATP site between different receptor kinases. However, a major breakthrough in this field was the discovery that 4-anilinoquinazolines are potent and selective inhibitors, despite binding at the ATP site. The very tight structure-activity relationships shown by these compds. suggested a clearly-defined binding mode, where the quinazoline ring binds in the adenine pocket and the anilino ring binds in an adjacent, unique lipophilic pocket. A unique cysteine (Cys-773) adjacent to the quinazoline binding site has prompted the development of irreversible inhibitors that target this residue. Three 4-anilinoquinazoline analogs (two reversible and one irreversible inhibitor) have been evaluated clin. as anticancer drugs. Data from the most advanced, the reversible inhibitor Iressa, suggest that this class of compds. may be of value in cancer chemotherapy.
IT **367518-74-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(4-anilinoquinazoline class of inhibitors of erbB family of receptor tyrosine kinases)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 21 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:380438 HCAPLUS
DOCUMENT NUMBER: 135:24657
TITLE: Selective cellular targeting: multifunctional delivery vehicles
INVENTOR(S): Glazier, Arnold
PATENT ASSIGNEE(S): Drug Innovation + Design, Inc., USA
SOURCE: PCT Int. Appl., 981 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036003	A2	20010525	WO 2000-US31262	20001114
WO 2001036003	C1	20020606		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165485P P 19991115
US 2000-239478P P 20001011
US 2000-241939P P 20001020

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

IT **341551-76-6P 341551-77-7P 341551-81-3P**
341552-85-0P
RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

L18 ANSWER 22 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:367797 HCAPLUS
DOCUMENT NUMBER: 135:102151
TITLE: Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in response to ErbB receptor family inhibition
AUTHOR(S): Nelson, James M.; Fry, David W.
CORPORATE SOURCE: Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Journal of Biological Chemistry (2001), 276(18), 14842-14847
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ErbB receptor family is implicated in the malignant transformation of several tumor types and is over-expressed frequently in breast, ovarian, and other tumors. The mechanism by which CI-1033 and gemcitabine, either singly or in combination, kill tumor cells was examd. in two breast lines, MDA-MB-453 and BT474; both overexpress the ErbB-2 receptor. CI-1033, a potent inhibitor of the ErbB family of receptor tyrosine kinases, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. Gemcitabine treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after gemcitabine produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined treatment p38 remained activated, whereas Akt and activated MAPK were

suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-kinase inhibitor LY294002 and the MAPK/ERK kinase inhibitor PD098059 in combination with gemcitabine produced the same results as the combination of CI-1033 and gemcitabine. P38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38 under unstressed conditions as well as activated Akt and MAPK. Treatment of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. Gemcitabine did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence of activated p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and gemcitabine in MDA-MB-453 cells. Furthermore, tumors that depend on ErbB receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as a single agent.

IT **267243-28-7**, CI-1033
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in human breast carcinoma in response to ErbB receptor family inhibition)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 23 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:338332 HCAPLUS
DOCUMENT NUMBER: 134:336209
TITLE: EGFR tyrosine kinase inhibitors for the prevention of breast cancer
INVENTOR(S): Bundred, Nigel James
PATENT ASSIGNEE(S): The University of Manchester, UK
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032155	A2	20010510	WO 2000-GB4190	20001101
WO 2001032155	A3	20020510		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000015194	A	20020618	BR 2000-15194	20001101
NO 2002002065	A	20020624	NO 2002-2065	20020430

PRIORITY APPLN. INFO.: GB 1999-25958 A 19991102
WO 2000-GB4190 W 20001101

AB An EGFR tyrosine kinase inhibitor (e.g. ZD1839) is used in the manuf. of a medicament for use in (a) reducing the transformation of epithelial cells from a normal to a malignant state in an invasive breast cancer free human; and/or (b) reducing the transformation of epithelial cells from an intermediate state, between normal epithelium and malignant invasive epithelium, to a malignant state in an invasive breast cancer free human; and/or (c) causing substantial reversion of epithelial tissue back to a normal state from an intermediate state between normal epithelium and malignant invasive epithelium.

IT **289499-45-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(EGFR tyrosine kinase inhibitors for the prevention of breast cancer)

L18 ANSWER 24 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:137057 HCAPLUS
DOCUMENT NUMBER: 134:173040
TITLE: NSAID- and EGFR kinase inhibitor-containing composition for the treatment or inhibition of colonic polyps and colorectal cancer
INVENTOR(S): Frost, Philip; DiScafani-Marro, Carolyn Mary
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012227	A1	20010222	WO 2000-US21021	20000802
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000013219	A	20020423	BR 2000-13219	20000802
EP 1202746	A1	20020508	EP 2000-950930	20000802
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
US 6432979	B1	20020813	US 2000-634787	20000809
NO 2002000663	A	20020409	NO 2002-663	20020211

PRIORITY APPLN. INFO.: US 1999-373261 A 19990812
US 1999-198212P P 19990812
WO 2000-US21021 W 20000802
OTHER SOURCE(S): MARPAT 134:173040
AB A method is provided for treating or inhibiting colonic polyps or colorectal cancer in a mammal in need thereof which comprises administering an NSAID and an EGFR kinase inhibitor. A NSAID, sulindac, and an EGFR kinase inhibitor, N-[4-((3-bromophenyl)amino)6-quinazolinyl]-2-butynamide, showed synergistic activity in redn. of intestinal polyps in an animal model.
IT **326894-84-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NSAID- and EGFR kinase inhibitor-contg. compn. for treatment of colon polyps and colorectal cancer)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 25 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:125550 HCAPLUS
DOCUMENT NUMBER: 134:348032
TITLE: The HER tyrosine kinase inhibitor CI1033 enhances cytotoxicity of 7-ethyl-10-hydroxycamptothecin and

topotecan by inhibiting breast cancer resistance protein-mediated drug efflux

AUTHOR(S): Erlichman, Charles; Boerner, Scott A.; Hallgren, Christopher G.; Spieker, Rebecca; Wang, Xiao-Yang; James, C. David; Scheffer, George L.; Maliepaard, Marc; Ross, Douglas D.; Bible, Keith C.; Kaufmann, Scott H.

CORPORATE SOURCE: Division of Medical Oncology, Mayo Clinic, Mayo Graduate School, Rochester, MN, 55905, USA

SOURCE: Cancer Research (2001), 61(2), 739-748
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Because the activities of HER family members are elevated and/or aberrant in a variety of human neoplasms, these cell surface receptors are receiving increasing attention as potential therapeutic targets. In the present study, we examd. the effect of combining the HER family tyrosine kinase inhibitor CI1033 (PD 183805) with the topoisomerase (topo) I poison 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan, in a no. of different cell lines. Colony-forming assays revealed that the antiproliferative effects of simultaneous treatment with CI1033 and SN-38 were synergistic in T98G glioblastoma cells and HCT8 colorectal carcinoma cells, whereas sequential treatments were additive at best. In addnl. studies examg. the mechanistic basis for these findings in T98G cells, immunoblotting revealed that the inhibitory effects of CI1033 on epidermal growth factor receptor autophosphorylation were unaffected by SN-38. Likewise, CI1033 had no effect on topo I polypeptide levels, localization, or activity. Nonetheless, CI1033 markedly enhanced the no. of covalent topo I-DNA complexes stabilized by SN-38 or the related agent topotecan (TPT). Anal. of intracellular SN-38 levels by high-performance liq. chromatog. and intracellular TPT levels by flow microfluorometry revealed that CI1033 increased the steady-state accumulation of SN-38 and TPT by 9.4 .+-. 1.9- and 1.8 .+-. 0.2-fold, resp. Further evaluation revealed that the initial rate of TPT uptake was unaffected by CI1033, whereas the rate of efflux was markedly diminished. Addnl. studies demonstrated that T98G and HCT8 cells express the breast cancer resistance protein (BCRP), a recently cloned ATP binding cassette transporter. Moreover, CI1033 enhanced the uptake and cytotoxicity of SN-38 and TPT in cells transfected with BCRP but not empty vector. Conversely, CI1033 accumulation was diminished in cells expressing BCRP, suggesting that CI1033 is a substrate for this efflux pump. These results indicate that CI1033 can modulate the accumulation and subsequent cytotoxicity of two widely used topo I poisons in cells that have no history of previous exposure to these agents.

IT **289499-45-2**, CI 1033
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(HER tyrosine kinase inhibitor CI1033 interactions with SN-38 and topotecan in cancer treatment)

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 26 OF 39 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:828300 HCAPLUS

DOCUMENT NUMBER: 135:57892

TITLE: Radiosensitization of human breast cancer cells by a novel ErbB family receptor tyrosine kinase inhibitor

AUTHOR(S): Rao, G. S.; Murray, S.; Ethier, S. P.

CORPORATE SOURCE: Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (2000), 48(5), 1519-1528
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: Overexpression of the ErbB family of growth factor receptors is present in a wide variety of human tumors and is correlated with poor prognosis. The purpose of this study was to det. the effects of a novel small mol. ErbB tyrosine kinase inhibitor, CI-1033, in combination with ionizing radiation on breast cancer cell growth and survival. Materials & Methods: Growth assays were performed on ErbB-overexpressing human breast cancer cells developed in our lab. in the presence of 0.1-1.0 .mu.M CI-1033 (Parke Davis). Clonogenic survival assays were performed in the presence of ionizing radiation with or without CI-1033. For some expts., clonogen nos., defined as the product of surviving fraction and total no. of cells, were calcd. at each time point during a course of multifraction radiation. Results: CI-1033 potently inhibited the growth of ErbB-overexpressing breast cancer cells. A single 48-h exposure of 1 .mu.M CI-1033 resulted in growth inhibition for 7 days, whereas three times weekly administration resulted in sustained growth inhibition. Clonogenic survival was modestly decreased after a 7-day exposure to CI-1033. Exposure to both CI-1033 and radiation (6 Gy) yielded a 23-fold decrease in clonogenic survival compared to radiation alone. In a multifraction expt., exposure to CI-1033 and three 5-Gy fractions of gamma radiation decreased the total no. of clonogens in the population by 65-fold compared to radiation alone. Conclusion: CI-1033 results in potent growth inhibition and modest cytotoxicity of ErbB-overexpressing breast cancer cells, and has synergistic effects when combined with ionizing radiation. These data suggest that CI-1033 may have excellent clin. potential both alone and in combination with radiation therapy.

IT **267243-28-7**, CI-1033
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiosensitization of human breast cancer cells by ErbB family receptor tyrosine kinase inhibitor)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 27 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:814464 HCAPLUS
DOCUMENT NUMBER: 133:362712
TITLE: Preparation of quinoline derivatives as inhibitors of MEK enzymes
INVENTOR(S): Boyle, Francis Thomas; Gibson, Keith Hopkinson; Poyser, Jeffrey Philip; Turner, Paul
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000068201	A1	20001116	WO 2000-GB1697	20000503

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,

ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1178967	A1	20020213	EP 2000-927491	20000503
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010391	A	20020702	BR 2000-10391	20000503
NO 2001005448	A	20020107	NO 2001-5448	20011107

PRIORITY APPLN. INFO.: GB 1999-10577 A 19990508
WO 2000-GB1697 W 20000503

OTHER SOURCE(S): MARPAT 133:362712
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. [I; or a pharmaceutically acceptable salt thereof wherein: n is 0-1; X and Y are independently selected from NH, O, S, or NR8 where R8 is alkyl of 1-6 carbon atoms and X may addnl. comprise a CH2 group; R7 is a group (CH2)mR9 where m is 0, or an integer of from 1-3 and R9 is a substituted aryl group, an optionally substituted cycloalkyl ring of up to 10 carbon atoms, or an optionally substituted heterocyclic ring or an N-oxide of any nitrogen contg. ring; R6 is a divalent cycloalkyl of 3 to 7 carbon atoms, which may be optionally further substituted with one or more alkyl of 1 to 6 carbon atom groups; or is a divalent pyridinyl, pyrimidinyl, or Ph ring; wherein the pyridinyl, pyrimidinyl, or Ph ring may be optionally further substituted with one or more specified groups; R1, R2, R3 and R4 are each independently selected from hydrogen or various specified org. groups]. Title compds. are useful as pharmaceuticals for the inhibition of MEK activity. Thus, the title compd. II was prepd. and tested in HT29 human colon tumor cell proliferation assay.

IT **307333-56-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of quinoline derivs. as inhibitors of MEK enzymes)

IT **307333-60-4P 307353-66-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of quinoline derivs. as inhibitors of MEK enzymes)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 28 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:670096 HCAPLUS
DOCUMENT NUMBER: 134:262
TITLE: Combinatorial chemoprevention of intestinal neoplasia
AUTHOR(S): Torrance, Christopher J.; Jackson, Peta E.; Montgomery, Elizabeth; Kinzler, Kenneth W.; Vogelstein, Bert; Wissner, Allan; Nunes, Maria; Frost, Philip; Discafani, Carolyn M.
CORPORATE SOURCE: Howard Hughes Med. Inst., Johns Hopkins Oncol. Cent., Baltimore, MD, 21231, USA
SOURCE: Nature Medicine (New York) (2000), 6(9), 1024-1028
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A combination of two drugs afforded remarkable protection from intestinal

neoplasia in APCMin/+ mice, a murine model of human familial adenomatous polyposis (FAP). One of the drugs was sulindac, a prototypical non-steroidal anti-inflammatory drug with established chemopreventive activity. The second drug was EKB569, a newly developed, irreversible inhibitor of the epidermal growth factor receptor kinase. Although 100% of the untreated APCMin/+ mice developed ~20 polyps, nearly half the mice treated with these two agents developed no polyps at all. These results suggest a powerful strategy for the chemoprevention of human colonic neoplasia.

IT **257933-82-7**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(EKB 569; intestinal neoplasia chemoprevention)

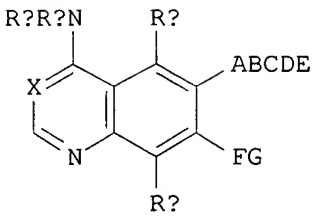
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 29 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:607393 HCAPLUS
DOCUMENT NUMBER: 133:207916
TITLE: Preparation of aminoquinazolines as epidermal growth factor receptor inhibitors.
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K-G, Germany
SOURCE: Ger. Offen., 26 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19908567	A1	20000831	DE 1999-19908567	19990227
WO 2000051991	A1	20000908	WO 2000-EP1496	20000224
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1157011	A1	20011128	EP 2000-910695	20000224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008524	A	20011218	BR 2000-8524	20000224
NO 2001004114	A	20011015	NO 2001-4114	20010824

PRIORITY APPLN. INFO.:
DE 1999-19908567 A 19990227
DE 1999-19911366 A 19990315
DE 1999-19928306 A 19990621
US 1999-149329P P 19990817
DE 1999-19954816 A 19991113
WO 2000-EP1496 W 20000224

OTHER SOURCE(S): MARPAT 133:207916
GI



I

AB Title compds. [I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH2, 1-phenylethyl; Rc, Rm = H, F, Cl, MeO, (methoxy-, dimethylamino-, diethylamino-, pyrrolidino-, piperidino-, morpholino- substituted) Me; X = N, NCC; A = O, alkylimino; B = CO, SO2; C = (Me- or F3C-substituted) allenylene, vinylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, etc.; E, G = (substituted) R6O2CYNR5, etc.; R5 = H, (substituted) alkyl; R6 = H, (substituted) alkyl, cycloalkyl, alkenyl, alkynyl, etc.; F = alkylene, oxyalkylene, O; FG = H, F, Cl, alkoxy, etc.], were prepd. Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-[4-(ethoxycarbonyl)methylpiperazin-1-yl]propoxy]quinazoline (prepn. given) in CH2Cl2 contg. Et3N was treated with acryloyl chloride in CH2Cl2 at -10.degree. to give 62% 4-[(3-bromophenyl)amino]-7-[3-[4-[(ethoxycarbonyl)methyl]piperazin-1-yl]propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation with IC50 = 2.6 nM.

IT **289700-58-9P 289700-59-0P 289700-60-3P**
289700-61-4P 289700-62-5P 289700-63-6P
289700-64-7P 289700-65-8P 289700-66-9P
289700-67-0P 289700-69-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoquinazolines as epidermal growth factor receptor inhibitors)

L18 ANSWER 30 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:481416 HCAPLUS
DOCUMENT NUMBER: 134:216784
TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. [Erratum to document cited in CA132:317628]
AUTHOR(S): Smaill, Jeff B.; Rewcastle, Gordon W.; Bridges, Alexander J.; Zhou, Hairong; Showalter, H. D. Hollis; Fry, David W.; Nelson, James M.; Sherwood, Veronika; Elliott, William L.; Vincent, Patrick W.; DeJohn, Dana E.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty Medical and Health Sciences, The Univ. Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (2000), 43(16), 3199
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Six author names were inadvertently omitted from the author contribution line. The complete author list is as follows: Jeff B. Smaill, Gordon W. Rewcastle, Alexander J. Bridges, Hairong Zhou, H. D. Hollis Showalter,

David W. Fry, James M. Nelson, Veronika Sherwood, William L. Elliott, Patrick W. Vincent, Dana E. DeJohn, Joseph A. Loo, Kenneth D. Greis, O. Helen Chan, Eric L. Reyner, Elke Lipka, and William A. Denny.

IT **198959-99-8P 198960-00-8P 198960-01-9P 198960-02-0P 198960-04-2P 198960-05-3P 267243-27-6P 267243-28-7P 267243-29-8P**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines (Erratum))

L18 ANSWER 31 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:368316 HCAPLUS
DOCUMENT NUMBER: 133:4672
TITLE: Preparation of N-{4-(3-chloro-4-fluorophenylamino)-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}acrylamide as an irreversible inhibitor of tyrosine kinases
INVENTOR(S): Bridges, Alexander James; Driscoll, Denise; Klohs, Wayne Daniel
PATENT ASSIGNEE(S): Warner-Lambert Co., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000031048	A1	20000602	WO 1999-US22116	19990923
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9962612	A1	20000613	AU 1999-62612	19990923
BR 9915487	A	20010731	BR 1999-15487	19990923
EP 1131304	A1	20010912	EP 1999-949821	19990923
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002530386	T2	20020917	JP 2000-583876	19990923
US 6344455	B1	20020205	US 2001-831991	20010516
NO 2001002465	A	20010713	NO 2001-2465	20010518

PRIORITY APPLN. INFO.: US 1998-109065P P 19981119
WO 1999-US22116 W 19990923

AB The title compd. that is an irreversible inhibitor of tyrosine kinases such as EGFR, erbB2, and erbB4, and inhibitor of the tyrosine phosphorylation of erbB3 and VEGF secretion (biol. data were given), was prepd. The title compd. is useful in treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis.

IT **198959-99-8P 267243-28-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-{4-(3-chloro-4-fluorophenylamino)-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}acrylamide as an irreversible inhibitor of tyrosine kinases)

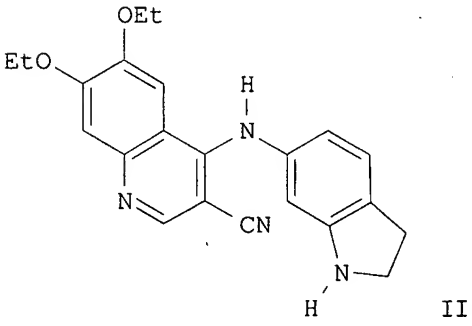
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:227652 HCAPLUS
DOCUMENT NUMBER: 132:265101
TITLE: Preparation of 3-cyanoquinolines as protein tyrosine kinase inhibitors
INVENTOR(S): Wissner, Allan; Tsou, Hwei-Ru; Berger, Dan Maarten; Floyd, Middleton Brawner, Jr.; Hamann, Philip Ross; Zhang, Nan; Salvati, Mark Ernest; Frost, Philip
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: PCT Int. Appl., 195 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018761	A1	20000406	WO 1999-US22054	19990922
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9961593	A1	20000417	AU 1999-61593	19990922
EP 1117659	A1	20010725	EP 1999-948410	19990922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525369	T2	20020813	JP 2000-572221	19990922
NO 2001001575	A	20010528	NO 2001-1575	20010328

PRIORITY APPLN. INFO.: US 1998-162802 A 19980929
WO 1999-US22054 W 19990922

OTHER SOURCE(S): MARPAT 132:265101
GI



II

AB X(CH2)nZZ1CN [I; X = (un)substituted bicyclic (hetero)aryl or LTA; A = (un)substituted phenylene, -pyridinediyl, -pyrimidinediyl; T = O, S, (alkyl)imino(alkylene), oxyalkylene, etc.; Z = O, S, (alkyl or alkanoyl)imino; Z1 = 2-unsubstituted-5,6,7,8-(un)substituted quinoline-4,3-diyl; n = 0 or 1] were prepd. Thus, Me 2-amino-4,5-diethoxybenzoate was N-condensed with HCNMe2/POCl3 and the product

cyclocondensed with MeCN to give, after POCl3 treatment, 4-chloro-6,7-diethoxyquinoline-3-carbonitrile which was aminated by 6-aminoindoline to give title compd II. Data for biol. activity of I were given.

IT **263170-75-8P 263170-78-1P 263170-81-6P**
263170-84-9P 263170-88-3P 263170-91-8P
263171-07-9P 263171-10-4P 263171-15-9P
263171-29-5P 263171-32-0P 263171-35-3P
263171-38-6P 263171-44-4P 263171-48-8P
263171-49-9P 263171-50-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-cyanoquinolines as protein tyrosine kinase inhibitors)

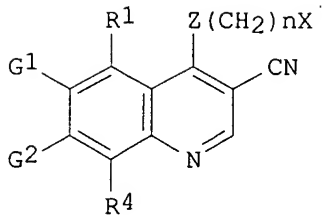
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 33 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:227636 HCAPLUS
DOCUMENT NUMBER: 132:265100
TITLE: Preparation of substituted 3-cyanoquinolines as protein tyrosine kinases inhibitors
INVENTOR(S): Wissner, Allan; Tsou, Hwei-Ru; Berger, Dan Maarten; Floyd, Middleton Brawner, Jr.; Hamann, Philip Ross; Zhang, Nan; Frost, Philip
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: PCT Int. Appl., 164 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018740	A1	20000406	WO 1999-US22056	19990922
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9961594	A1	20000417	AU 1999-61594	19990922
BR 9914164	A	20010626	BR 1999-14164	19990922
EP 1117649	A1	20010725	EP 1999-948411	19990922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002525359	T2	20020813	JP 2000-572200	19990922
NO 2001001574	A	20010528	NO 2001-1574	20010328

PRIORITY APPLN. INFO.: US 1998-162289 A 19980929
WO 1999-US22056 W 19990922

OTHER SOURCE(S): MARPAT 132:265100
GI



I

AB The title compds. I [X = cycloalkyl, pyridinyl, pyrimidinyl, etc.; Z = NH, O, S, NR; G1, G2, R1, R4 = H, halo, alkyl, alkynyl, etc.; n = 0,1], protein tyrosine kinase inhibitors, were prepd. E.g., 4-(2-methoxyethoxy)but-2-ynoic acid [4-(3-bromophenylamino)-3-cyanoquinolin-6-yl]amide was prepd. I are useful as antineoplastic agents.

IT **263149-00-4P 263149-01-5P 263149-02-6P**
263149-03-7P 263149-04-8P 263149-06-0P
263149-07-1P 263149-08-2P 263149-13-9P
263149-14-0P 263149-16-2P 263149-17-3P
263149-18-4P 263149-19-5P 263149-20-8P
263149-26-4P 263149-30-0P 263149-44-6P
263149-45-7P 263149-46-8P 263149-47-9P
263149-90-2P 263150-04-5P 263150-31-8P
263150-32-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of cyanoquinolines as protein tyrosine kinase inhibitors)

IT **263149-21-9P 263149-22-0P 263149-23-1P**
263149-24-2P 263149-25-3P 263149-27-5P
263149-28-6P 263149-29-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of cyanoquinolines as protein tyrosine kinase inhibitors)

IT **263150-36-3P 263150-38-5P 263150-40-9P**
263150-42-1P 263150-44-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of cyanoquinolines as protein tyrosine kinase inhibitors)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 34 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:164843 HCAPLUS
DOCUMENT NUMBER: 132:317628
TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions
AUTHOR(S): Smaill, Jeff B.; Rewcastle, Gordon W.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Showalter, H. D. Hollis; Vincent, Patrick W.; Elliott, William L.; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (2000), 43(7), 1380-1397
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English

AB 4-Anilinoquinazoline- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains were prepd. by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido[3,2-d]pyrimidine series, the intermediate 6-amino-7-alkylamines were prepd. from 7-bromo-6-fluoropyrido[3,2-d]pyrimidine via Stille coupling with the appropriate stannane under palladium(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compds. were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogs with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC50[app] values from 2 to 4 nM, and potently inhibited both EGFR and erbB2 autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyaminopyrido[3,2-d]pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido[3,2-d]pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A comparison of two 7-propoxymorpholide analogs showed that the pyrido[3,2-d]pyrimidine-6-acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference may contribute to the obsd. lower cellular potency of the pyrido[3,2-d]pyrimidine-6-acrylamides. Selected compds. showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido[3,2-d]pyrimidines. Overall, the quinazolines proved superior to previous analogs in terms of aq. soly., potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clin. evaluation.

IT **198959-99-8P 198960-00-8P 198960-01-9P**
198960-02-0P 198960-04-2P 198960-05-3P
267243-27-6P 267243-28-7P 267243-29-8P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 35 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:794373 HCAPLUS
DOCUMENT NUMBER: 132:35620
TITLE: Preparation of substituted 3-cyanoquinolines as inhibitors of growth factor receptor protein tyrosine kinases (PTK)
INVENTOR(S): Wissner, Allan; Johnson, Bernard D.; Reich, Marvin F.; Floyd, Middleton B. , Jr.; Kitchen, Douglas B.; Tsou, Hwei-ru
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: U.S., 80 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 6002008	A	19991214	US 1998-49718	19980327
PRIORITY APPLN. INFO.:			US 1997-41963P P	19970403
OTHER SOURCE(S):	MARPAT 132:35620			

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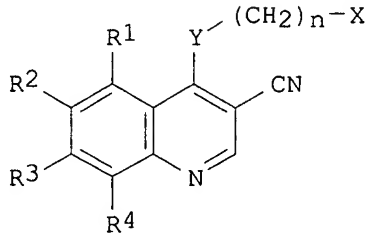
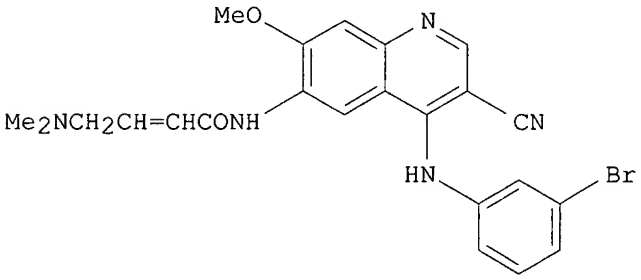


I



II

AB This invention provides compds. having the formula (I; wherein: X is cycloalkyl which may be optionally substituted; or is a pyridinyl, pyrimidinyl, or Ph ring; wherein the pyridinyl, pyrimidinyl, or Ph ring may be optionally substituted; n is 0-1; Y is NH, O, S, or NR; R is alkyl of 1-6 carbon atoms; R1, R2, R3, and R4 are each, independently, hydrogen, halogen, alkyl, alkenyl, alkynyl, alkenyloxy, alkynoyloxy, hydroxymethyl, halomethyl, alkanoyloxy, alkenoyloxy, alkynyloxy, alkanoyloxymethyl, alkenoyloxymethyl, alkynoyloxymethyl, alkoxymethyl, alkoxy, alkylthio, alkylsulphinyl, alkylsulfonyl, alkylsulfonamido, alkenylsulfonamido, alkynylsulfonamido, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy, carboalkyl, phenoxy, Ph, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino, alkylamino, dialkylamino, aminoalkyl, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, phenylamino, benzylamino, etc.; R5 is alkyl which may be optionally substituted, or Ph which may be optionally substituted; R6 is hydrogen, alkyl, or alkenyl; R7 is chloro or bromo; R8 is hydrogen, alkyl, aminoalkyl, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, N-cycloalkylaminoalkyl, N-cycloalkyl-N-alkylaminoalkyl, N,N-dicycloalkylaminoalkyl, morpholino-N-alkyl, piperidino-N-alkyl, N-alkyl-piperidino-N-alkyl, azacycloalkyl-N-alkyl, hydroxyalkyl, alkoxyalkyl, carboxy, carboalkoxy, Ph, carboalkyl, chloro, fluoro, or bromo; Z is amino, hydroxy, alkoxy, alkylamino, dialkylamino). The compds. of the present invention inhibit the action of certain growth factor receptor protein tyrosine kinases (PTK) thereby inhibiting the abnormal growth of certain cell types. They are therefore useful for the treatment of certain diseases that are the result of deregulation of these PTKs, in particular as anti-cancer agents for the treatment of cancers expressing epidermal growth factor receptor (EGFR), mitogen activated protein kinase (MAPK), epithelial kinase (ECK), and kinase insert domain contg. receptor (KDR) in mammals and for the treatment of polycystic kidney disease in mammals. Thus, To a mixt. of 1.9 g (5.1 mmol) of 4-[(3-bromophenyl)amino]-7-methoxy-6-amino-3-quinolinecarbonitrile and 5.3 mL (31 mmol) of Hunig's base in 110 mL of dry THF at 0.degree. C., with

stirring, was added a THF soln. contg. 5.7 g (31 mmol) of 4-bromocrotonyl chloride dropwise. The mixt. was stirred for addnl. 0.5 h. After addn. 100 mL of satd. sodium chloride soln. was added to the reaction mixt., then it was extd. with Et acetate. The Et acetate soln. was dried over sodium sulfate and then was added to 40 mL of di-Me amine soln. (2.0 M in THF) at 0.degree. dropwise and stirred an addnl. 0.5 h to give 4-Dimethylamino-but-2-enoic acid [4-(3-bromo-phenylamino)-3-cyano-7-methoxy-quinolin-6-yl]amide (II). II showed IC50 of 0.000008 .mu.M against epidermal growth factor receptor kinase.

IT **214484-05-6P 214484-07-8P 214485-38-8P**
214485-56-0P 214485-57-1P 214485-58-2P
214485-61-7P 214485-62-8P 214485-63-9P
214485-66-2P 214485-67-3P 214485-70-8P
214485-71-9P 214485-72-0P 214485-73-1P
214485-80-0P 214486-79-0P 214486-80-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted 3-cyanoquinolines as inhibitors of growth factor receptor protein tyrosine kinases (PTK) for treatment of cancers and polycystic kidney disease)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 36 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:113672 HCAPLUS
DOCUMENT NUMBER: 130:182476
TITLE: Preparation of heterocyclic compounds as irreversible bicyclic inhibitors of tyrosine kinases
INVENTOR(S): Bridges, Alexander James
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906396	A1	19990211	WO 1998-US15592	19980729
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9886659	A1	19990222	AU 1998-86659	19980729
US 6153617	A	20001128	US 1999-269647	19990325

PRIORITY APPLN. INFO.: US 1997-54061P P 19970729
WO 1998-US15592 W 19980729

OTHER SOURCE(S): MARPAT 130:182476
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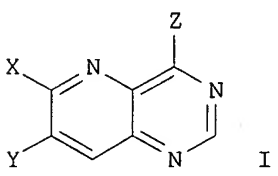

I

AB The title compds., e.g. I [X = DEF, Y = SR4, etc. ; or X = SR4, etc., and Y = DEF; D = O, etc.; E = CO, etc.; F = CR1(:C):C(R5)H, etc.; a proviso is given; R1 = H, halo, etc.; R5 = H, halo, perfluoroalkyl, etc.; Z = indoline moiety (generic structure given), etc.; R4 = H, alkyl, etc.], are prepd. This invention also provides a method of treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis and a pharmaceutical compn. that comprises a compd. that is an irreversible inhibitor of tyrosine kinases. N-[4-(6-bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide in vitro showed IC50 of 0.4 nM against epidermal growth factor receptor tyrosine kinase.

IT **220576-91-0P 220576-92-1P 220576-93-2P**
220576-94-3P 220577-98-0P 220578-00-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclic compds. as irreversible bicyclic inhibitors of tyrosine kinases)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 37 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:113656 HCAPLUS
DOCUMENT NUMBER: 130:168387
TITLE: Irreversible inhibitors of tyrosine kinases
INVENTOR(S): Bridges, Alexander James
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906378	A1	19990211	WO 1998-US15784	19980729
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9887607	A1	19990222	AU 1998-87607	19980729
US 6127374	A	20001003	US 1999-269545	19990325

PRIORITY APPLN. INFO.: US 1997-54060P P 19970729
WO 1998-US15784 W 19980729

OTHER SOURCE(S): MARPAT 130:168387

AB Pyrimidine derivs. that are irreversible inhibitors of tyrosine kinases are reported. Thus, PhCH2OH was treated with 4-FC6H4NO2 to give 4-PhCH2OC6H4NO2, which was reduced to the amine and used to aminate 4-chloro-6-nitroquinazoline hydrochloride. The resulting 6-nitro-4-(4-benzyloxyanilino)quinazoline hydrochloride was reduced to the amine and acylated to give N-[4-(4-benzyloxyanilino)quinazolin-6-yl]acrylamide (I). I had an IC50 for inhibition of epidermal growth factor receptor tyrosine kinase of 3.6 nM.

IT **220488-46-0P 220488-47-1P 220488-48-2P**
220488-49-3P 220489-87-2P 220489-88-3P
220489-89-4P 220489-90-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of anilinoquinazolinylacrylamides and related compds. as tyrosine kinase inhibitors)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 38 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:682233 HCAPLUS
DOCUMENT NUMBER: 129:302564
TITLE: Preparation of substituted 3-cyanoquinolines as inhibitors of protein tyrosine kinase
INVENTOR(S): Wissner, Allan; Johnson, Bernard Dean; Reich, Marvin Fred; Floyd, Middleton Brawner, Jr.; Kitchen, Douglas B.; Tsou, Hwei-ru
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: PCT Int. Appl., 223 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9843960	A1	19981008	WO 1998-US6480	19980402
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CN 1161330	A	19971008	CN 1997-101099	19970204
ZA 9802771	A	19991001	ZA 1998-2771	19980401
AU 9868777	A1	19981022	AU 1998-68777	19980402
AU 750906	B2	20020801		
EP 973746	A1	20000126	EP 1998-914417	19980402
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
JP 2001519788	T2	20011023	JP 1998-541981	19980402
NO 9904798	A	19991124	NO 1999-4798	19991001

PRIORITY APPLN. INFO.: US 1997-826604 A 19970403
WO 1998-US6480 W 19980402
OTHER SOURCE(S): MARPAT 129:302564
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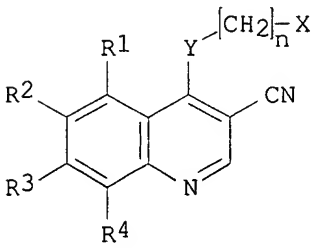

I

AB The title compds. [I; X = (un)substituted cycloalkyl, pyridinyl, pyrimidinyl, Ph; n = 0-1; Y = NH, O, S, NR; R = = C1-6 alkyl; R1-R4 = H,

halo, alkyl, etc. (with the proviso that when Y = NH; R1-R4 = H; n = O; X is not 2-methylphenyl)], inhibitors of protein tyrosine kinase which are useful in treating, inhibiting the growth of, or eradicating a neoplasm which expresses EGFR, MAPK, ECK or KDR, and in treating polycystic kidney disease, were prepd. Thus, treatment of 2-butynoic acid with iso-Bu chloroformate and N-methylmorpholine in THF followed by the addn. of this soln. of the mixed anhydride to a soln. of 6-amino-4-[(3-bromophenyl)amino]-7-methoxy-3-quinolinecarbonitrile (prepn. described) in THF over a 24 h period afforded I [Y = NH; n = 0; X = 3-BrC6H4; R1 = R4 = H; R2 = MeC.tplbond.CC(O)NH; R3 = MeO] which showed IC50 of 0.15 .mu.M against epidermal growth factor receptor kinase (A431 membrane ext.).

IT **214484-05-6P 214484-07-8P 214485-38-8P**
214485-56-0P 214485-57-1P 214485-58-2P
214485-61-7P 214485-62-8P 214485-63-9P
214485-66-2P 214485-67-3P 214485-70-8P
214485-71-9P 214485-72-0P 214485-73-1P
214485-80-0P 214486-79-0P 214486-80-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted 3-cyanoquinolines as inhibitors of protein tyrosine kinase)

L18 ANSWER 39 OF 39 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:696745 HCAPLUS
DOCUMENT NUMBER: 128:3695
TITLE: Preparation of N-quinazolinylacrylamides and analogs as tyrosine kinase inhibitors
INVENTOR(S): Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; Mcnamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong; et al.
PATENT ASSIGNEE(S): Warner-Lambert Company, USA; Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; Mcnamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong
SOURCE: PCT Int. Appl., 193 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9738983	A1	19971023	WO 1997-US5778	19970408
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2249446	AA	19971023	CA 1997-2249446	19970408
AU 9724463	A1	19971107	AU 1997-24463	19970408
AU 725533	B2	20001012		
EP 892789	A1	19990127	EP 1997-920213	19970408
EP 892789	B1	20020227		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CN 1218456	A	19990602	CN 1997-194458	19970408
BR 9708640	A	19990803	BR 1997-8640	19970408

JP 2000508657	T2	20000711	JP 1997-537173		19970408
AT 213730	E	20020315	AT 1997-920213		19970408
ZA 9703060	A	19971104	ZA 1997-3060		19970410
NO 9804718	A	19981209	NO 1998-4718		19981009
KR 2000005364	A	20000125	KR 1998-8086		19981010
KR 2000005364	A	20000125	KR 1998-708086		19981010
US 6344459	B1	20020205	US 1999-155501		19990608
PRIORITY APPLN. INFO.:			US 1996-15351P	P	19960412
			WO 1997-US5778	W	19970408

OTHER SOURCE(S): MARPAT 128:3695
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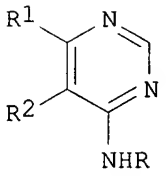

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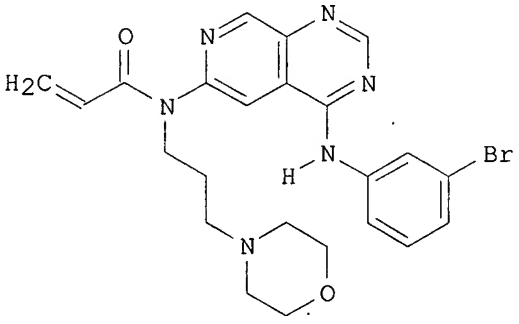

II

AB Title compds. [I; R = (CHR6)pR9; R1R2 = CH:CR7CR8:CH, CH:CR7CR8:N, CH:CR7N:CH, etc.; R6 = H or alkyl; 1 of R7,R8 = Z1Z2R10 and the other = OR4, SR4, NHR3; R3,R4 = (un)substituted alkyl, heterocyclylalkyl, etc.; R9 = (un)substituted Ph; R10 = CR11:CHR5, C.tplbond.CR5, CR11:C:CHR5; R5 = H, halo, alkyl, Ph, etc.; R11 = H, halo, alkyl; Z1 = bond, O, (alkyl)imino, CH2, etc.; Z2 = CO, SO, P(O)(OH), etc.; p = 0 or 1] were prepd. Thus, I (R = C6H4Br-3, R1R2 = CH:NCR8:CH, R8 = F) was condensed with 3-morpholinoprpanamine and the product acylated by CH2:CHCOCl to give title compd. II. Data for biol. activity of I were given.

IT **198959-99-8P 198960-00-8P 198960-01-9P**
198960-02-0P 198960-04-2P 198960-05-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-quinazolinylacrylamides and analogs as tyrosine kinase inhibitors)

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=> fil reg
FILE 'REGISTRY' ENTERED AT 16:06:57 ON 17 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 16 OCT 2002 HIGHEST RN 462058-01-1
DICTIONARY FILE UPDATES: 16 OCT 2002 HIGHEST RN 462058-01-1

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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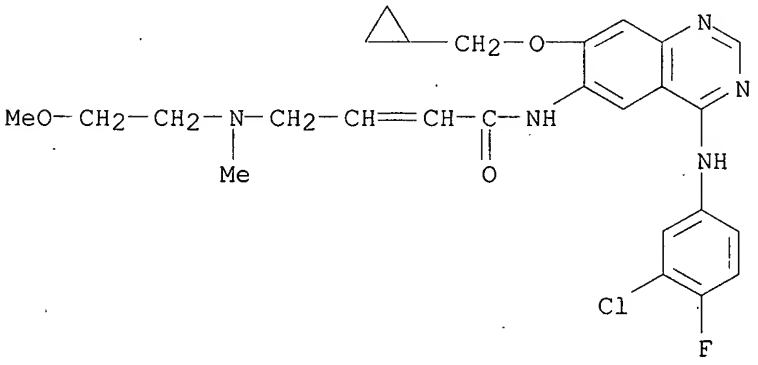
=> d ide can 117 1 25 50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 413

L17 ANSWER 1 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 439081-48-8 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2-methoxyethyl)methylamino]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C26 H29 Cl F N5 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:63250

L17 ANSWER 25 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 439081-21-7 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-3-furanyl)methoxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)
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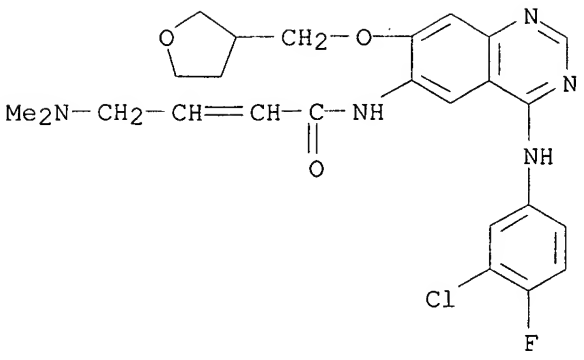
MF C25 H27 Cl F N5 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



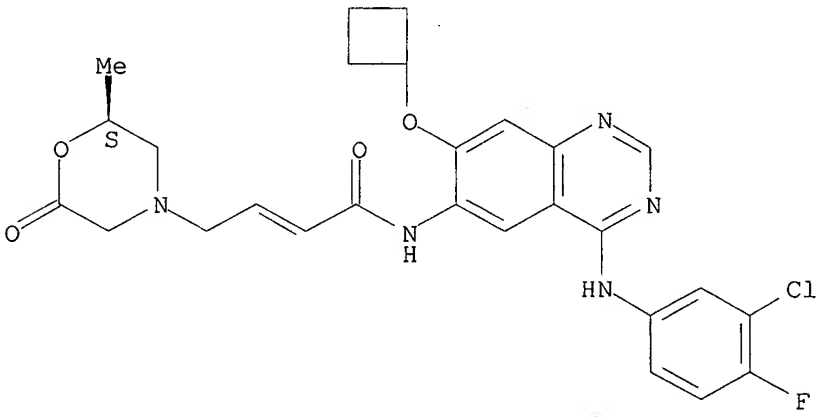
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:63250

L17 ANSWER 50 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 402855-55-4 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]-4-[(2S)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H27 Cl F N5 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry unknown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

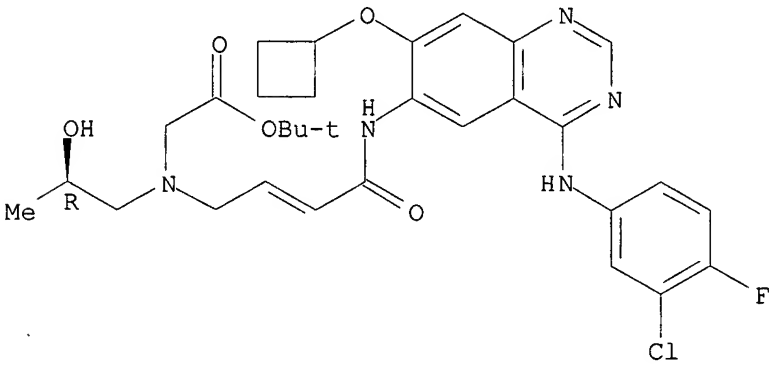
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:232315

L17 ANSWER 75 OF 413 REGISTRY COPYRIGHT 2002 ACS

RN 402855-21-4 REGISTRY
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H37 Cl F N5 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry unknown.

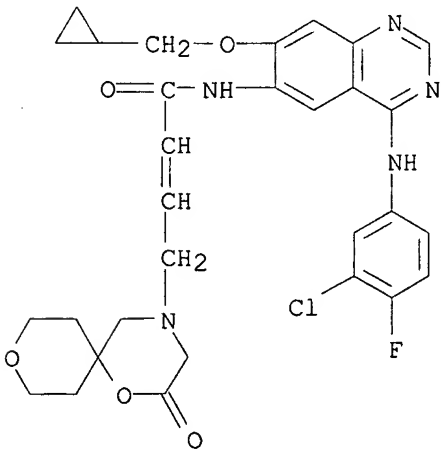


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:232315

L17 ANSWER 100 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 402569-99-7 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2-oxo-1,9-dioxa-4-azaspiro[5.5]undec-4-yl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C30 H31 Cl F N5 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:216762

L17 ANSWER 125 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 367282-07-3 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[1-(tetrahydro-2-oxo-3-furanyl)-4-piperidinyl]amino]- (9CI) (CA INDEX NAME)
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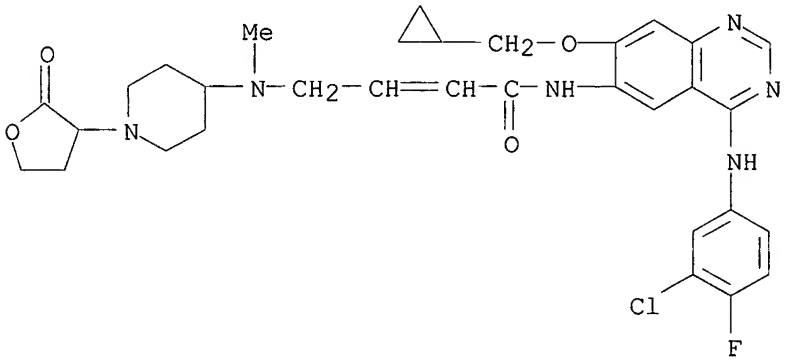
MF C32 H36 Cl F N6 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



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1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:303907

L17 ANSWER 150 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 341551-81-3 REGISTRY
CN 2-Propenamide, N-[7-(3-aminopropoxy)-4-[(3-chloro-4-fluorophenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)
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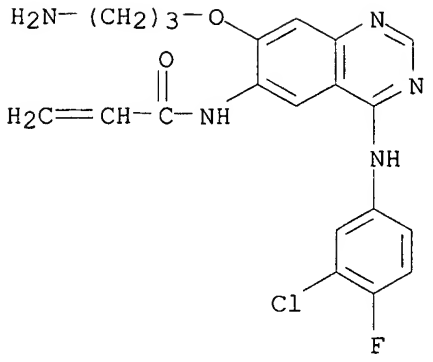
MF C20 H19 Cl F N5 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

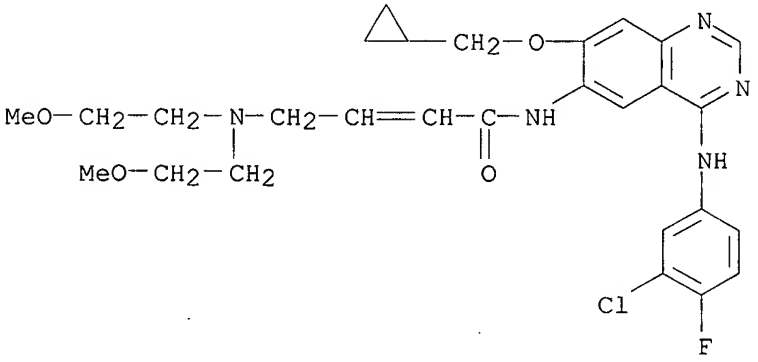


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:24657

L17 ANSWER 175 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 314771-48-7 REGISTRY
CN 2-Butenamide, 4-[bis(2-methoxyethyl)amino]-N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C28 H33 Cl F N5 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



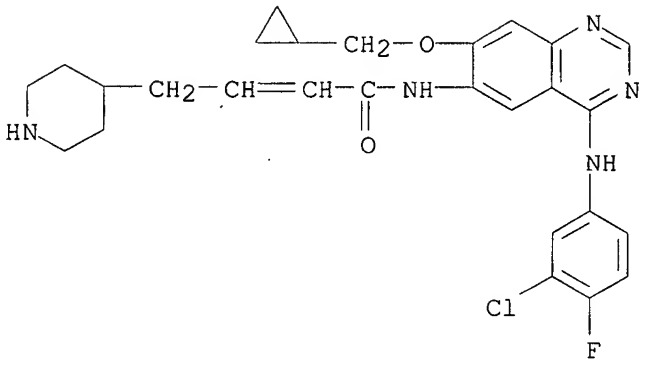
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71599

L17 ANSWER 200 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 314771-12-5 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(4-piperidinyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD

MF C27 H29 Cl F N5 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

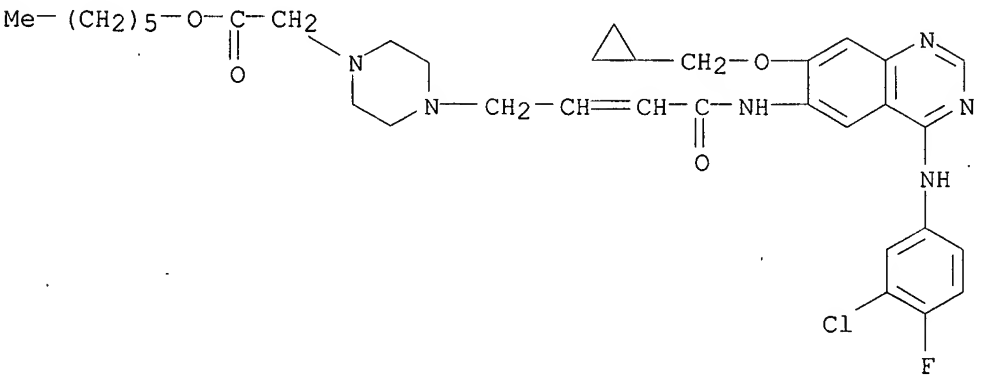


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:71599

L17 ANSWER 225 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 290303-10-5 REGISTRY
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, hexyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C34 H42 Cl F N6 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

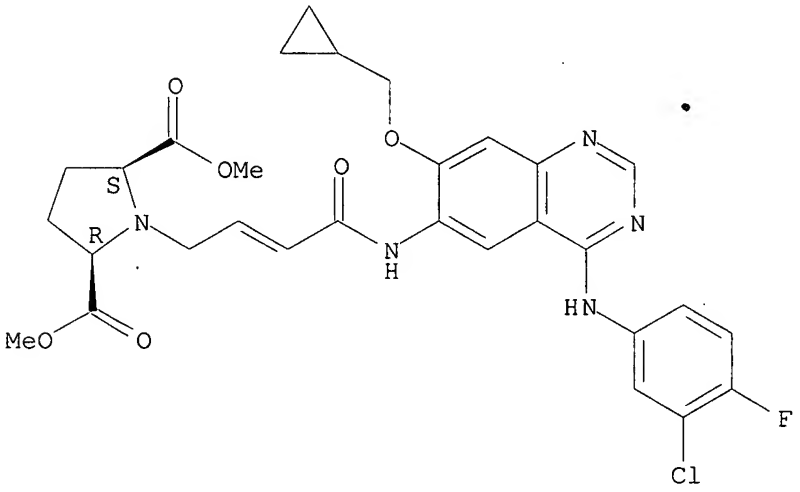
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 133:207919

L17 ANSWER 250 OF 413 REGISTRY COPYRIGHT 2002 ACS

RN 290302-63-5 REGISTRY
CN 2,5-Pyrrolidinedicarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, dimethyl ester, (2R,5S)-rel- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H31 Cl F N5 O6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Relative stereochemistry.
Double bond geometry unknown.

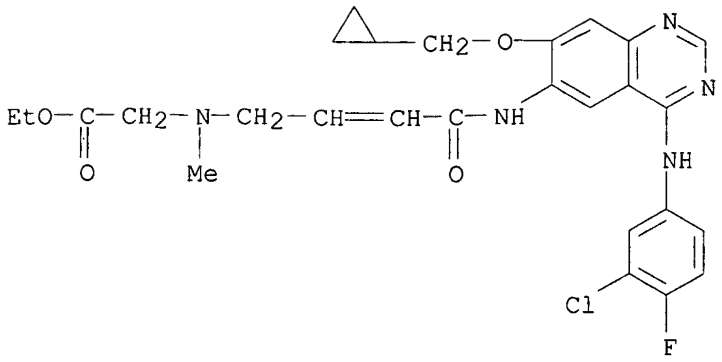


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 133:207919

L17 ANSWER 275 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 290302-09-9 REGISTRY
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H29 Cl F N5 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

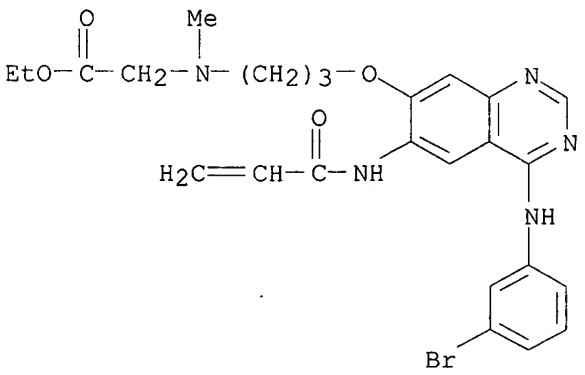


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 133:207919

L17 ANSWER 300 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 290301-64-3 REGISTRY
CN Glycine, N-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C25 H28 Br N5 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

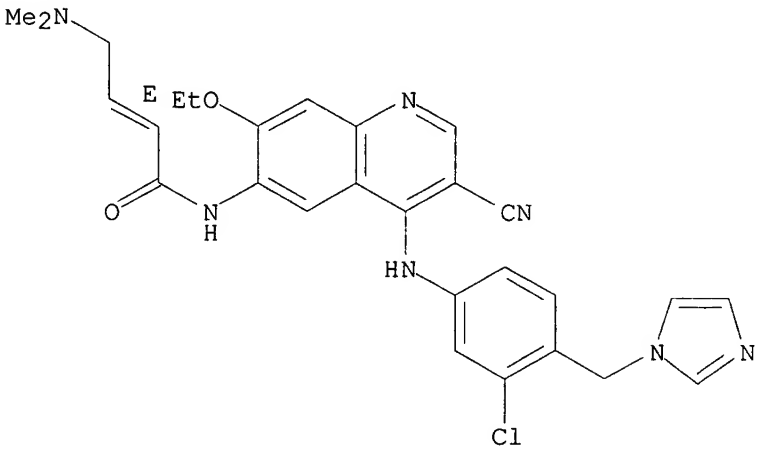
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 133:207919

L17 ANSWER 325 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 263171-32-0 REGISTRY
CN 2-Butenamide, N-[4-[[3-chloro-4-(1H-imidazol-1-ylmethyl)phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-, (2E)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C28 H28 Cl N7 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Double bond geometry as shown.



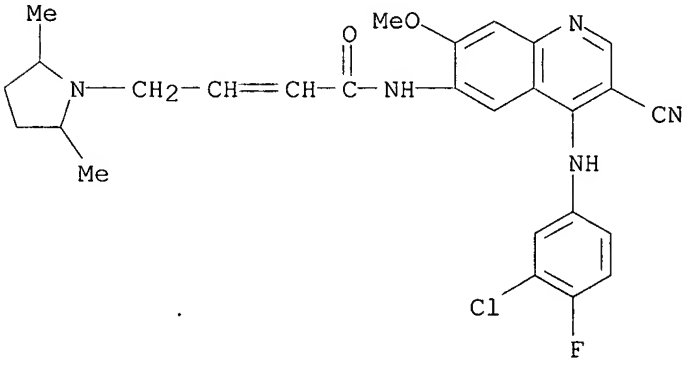
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:226901

REFERENCE 2: 132:265101

L17 ANSWER 350 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 263149-29-7 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl]-4-(2,5-dimethyl-1-pyrrolidinyl)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H27 Cl F N5 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)

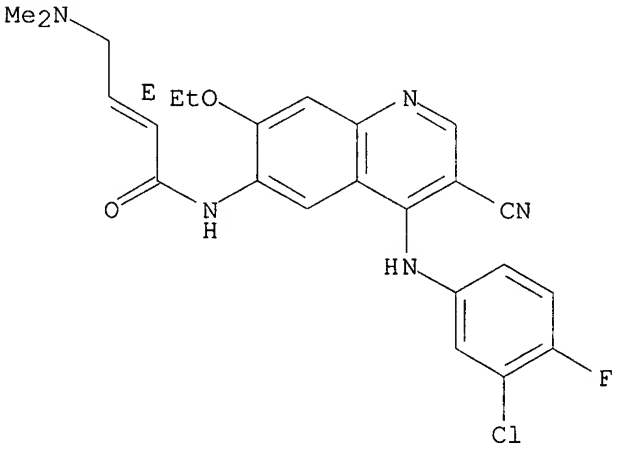
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:272896

REFERENCE 2: 132:265100

L17 ANSWER 375 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 257933-82-7 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-, (2E)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN EKB 569
CN WAY-EKB 569
FS STEREOSEARCH
MF C24 H23 Cl F N5 O2
SR CAS Registry Services
LC STN Files: BIOSIS, CA, CAPLUS, DRUGNL, DRUGUPDATES, TOXCENTER, USPATFULL

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

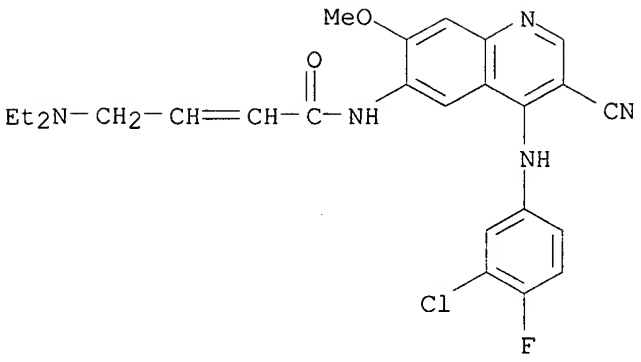
3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:134227

REFERENCE 2: 135:288636

REFERENCE 3: 134:262

L17 ANSWER 400 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 214485-62-8 REGISTRY
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-methoxy-6-quinolinyl]-4-(diethylamino)- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C25 H25 Cl F N5 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

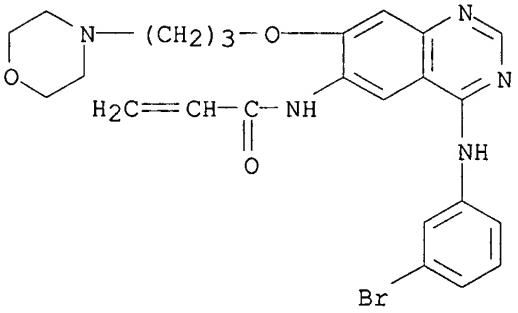
3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:242152

REFERENCE 2: 132:35620

REFERENCE 3: 129:302564

L17 ANSWER 413 OF 413 REGISTRY COPYRIGHT 2002 ACS
RN 198959-99-8 REGISTRY
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C24 H26 Br N5 O3
SR CA
LC STN Files: ADISINSIGHT, CA, CAPLUS, DRUGUPDATES, SYNTHLINE, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1962 TO DATE)
5 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:163829

REFERENCE 2: 134:216784

REFERENCE 3: 133:4672

REFERENCE 4: 132:317628

REFERENCE 5: 128:3695